UNIVERSITE DE LAUSANNE–FACULTE DE BIOLOGIE ET DE MEDECINE

Département de Neurosciences Cliniques
Service de Neurologie
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Severely Presenting Strokes: Profile & Outcome

THESE

préparée sous la direction du Dr. Patrik Michel

et présentée à la Faculté de biologie et de médecine de
l'Université de Lausanne pour l'obtention du grade de

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par

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Severely Presenting Strokes: Profile & Outcome

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Severely presenting Strokes: Profile & Outcome

MD thesis project

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Résumé:

Etat des connaissances:

Les Accidents vasculaires cérébraux (AVC) sévères sont une cause importante de mortalité et de handicap en Suisse. Les buts de cette étude sont de déterminer les caractéristiques des patients avec un AVC à présentation initiale sévère "severely presenting", ainsi que d'identifier les facteurs prédicteurs en phase aigüe et subaigüe d'un devenir favorable chez ces patients.

Methodologie:

En utilisant le registre des AVC "Acute STroke Registry and Analysis of Lausanne (ASTRAL), nous avons comparé tous les patients avec un AVC "à présentation sévère", defini comme un score National Institute of Health Stroke Scale (NIHSS) $\geq$ 20 à l'admission aux urgences, avec tous les autres patients du registre. Dans une analyse statistique multivariée, les associations avec les caractéristiques démographiques, cliniques, pathophysiologiques, métaboliques et radiologiques des patients on été determinées. Dans un deuxième temps, nous avons analysé les facteurs prédicteurs d'un devenir favorable à 3 mois (modified Rankin scale (mRS) $\leq$3) dans ce groupe d'AVC à présentation sévère.

Resultats:

Parmi les 1'915 patients consécutifs, 243 (12.7%) présentaient un AVC rejoignant la définition de sévère. Ceux-cis étaient associés de manière significative avec un méchanisme ischémique cardio-embolique (OR=1.74 / 95% CI 1.19 - 2.54), un début inconnu de la symptomatologie (OR=2.35 / 95% CI 1.14 - 4.83), avaient plus de trouvailles d'origine ischémique aigüe lors de l'imagerie d'entrée (la majorité sont des CT-scan, OR=2.65 / 95% CI 1.79 - 3.92), plus d'occlusions dans l'imagerie vasculaire d'admission (OR=27.01 / 95% CI 11.5 – 62.9), moins d'anciens infarctus cérébraux sur l'imagerie (OR=0.43 / 95% 0.26-0.72), un taux d'haemoglobine plus bas en g/l (OR=0.97 / 95% CI 0.96 - 0.99), un taux de leucocytes plus élevé par 1000 cells/l (OR=1.05 / 95%CI 1.00 - 1.11). parmi les 68 (28%) patients avec un devenir favorable malgré un AVC initialement sévère, leur évolution favorable à été associée avec un âge plus jeune (OR=0.94 / 95% CI 0.92 - 0.97), la présence d'évenements cérébrovasculaires antécédants (OR=3.00 / 95% CI 1.01 - 8.97), un traitement hypolipémiant déjà présent (OR= 3.82 / 95% CI 1.34 - 10.90), une température corporelle

d'admission plus basse (OR=0.43 / 95% CI 0.23 - 0.78), une concentration subaigüe de glucose plus basse (OR=0.74 / 95% CI 0.56 - 0.97), et une recanalisation spontanée ou par thrombolyse à 24h (OR= 4.51 / 95%CI 1.96 - 10.41).

Conclusion:

les AVC à présentation initiale sévère sont associés à des facteurs prédicteurs cliniques, radiologiques, et métaboliques multiples, dont certains sont modifiables. Les facteurs prédicteurs des 28% de patients avec un devenir favorable en dépit d'un AVC intitialement sévère sont un pré-traitement par hypolipémiants, une temperature corporelle plus basse à l'admission, une glycémie plus basse à 24heures et la recanalisation artérielle.

Travail de Thèse:

1. Background and current knowledge

1.1 Introduction

Acute ischemic stroke (AIS) is the third leading cause of death after cardiac diseases and cancer. In the industrialized world, stroke is also the most frequent cause of acquired disability in adults [1] [2]. With a prevalence of 300/100,000 patients per year stroke represents a major societal burden in terms of both mortality and on-going patient care. Interestingly in Switzerland, the overall crude mortality rates in 2006 were 25/100,000 in women and 31/100,000 in men which are among the lowest in the world[3].

1.2 Severely presenting strokes

"Severely presenting stroke" is defined by a National Institute of Health Stroke Scale (NIHSS) score ≥20, and is also known as malignant cerebral infarction if the total territory of the middle cerebral artery is infarcted. Malignant middle cerebral artery (MCA) territory strokes have a poor prognosis. This is partially due to the risk developing a cerebral oedema and herniation that can lead to coma or brain death, which happens more often in young patients [30-31]. They often present with early reduced consciousness and progress to coma and brain death within 2 to 5 days in almost 80% of patients treated only with conservative medical therapy. Survivors of this form of stroke are severely disabled with poor quality of life [30]. Their incidence is estimated at 2-10% of all ischemic strokes[4]. Patients with malignant MCA infarction are also at increased risk of adverse outcome or death due to stroke-related complications such as pneumonia[5], acute cardiac failure[6].
A better knowledge of the risk factors and the relation between the patients' characteristics and their long term outcome would thus be useful towards patient management in the acute as well as subacute phase. Patients' information regarding their condition would be more accurate and research protocols concerning stroke would of course also benefit from these findings.

1.3 Etiology, mechanisms

Commonest stroke mechanisms are embolism, mainly from a cardiac source, or from extracranial arteries. Compared to less severe strokes, massive brain ischemia seems to be more often caused by cardiac emboli and less by large artery occlusive mechanisms.[7]

1.4 Imaging and localisation

Apart from the underlying pathophysiologic mechanism, neuroimaging is another means which may hold promise in identifying stroke patients with potentially worse outcomes. Non-contrast computed tomography (CT) is recommended in the acute phase of stroke to detect early ischemic changes suggestive of evolving ischemia and hypodensities which are highly predictive of completed infarction. [8-13]

1.5 Prognostic factors & Outcome

Initial stroke severity, hyperglycemia, increasing age, infarct volume, underlying cardio-embolic or dissection as pathophysiologic mechanism and fever [17, 18] are consistently associated with worse outcome. With less evidence, the following factors might predict worse functional recovery after stroke: poor pre-morbid status, cognitive impairment, reduced consciousness at onset, pre-existing hemiplegia, homonymous hemianopia, visual extinction, constructional apraxia, non-stroke unit care, visuospatial symptoms, urinary incontinence and female gender[19].The most robust predictors of disability at 5 years after stroke are increasing age, recurrent stroke, and severity at onset[20] The latter may be graded according to neurological scores such as NIHSS.

NIHSS score within 24hours after symptoms' onset is related to the volume of infarcted cerebral tissue measured on CT at 7 days[21]. The initial score allows a more reliable prediction of the residual disablement of a patient than other existing scales[22]. Its utilisation in large clinical trials has now helped to define thresholds, that still need confirmation by further work: a score <10 before the third hour predicts a 40% chance to fully recover, whereas complete recovery is almost never the case when this score is >20[23]. Moreover, previous work has shown that NIHSS score >15 within 24h after stroke onset leads to an increase of hemorrhagic transformation by 15% if the patient receives anticoagulation at therapeutic levels[24].

Some patients with initially severe strokes may show excellent recovery. The following may be useful markers of patients more likely to improve: young age, small lesion size, early arterial recanalisation (spontaeous or interventional), absence of pre-stroke disability, normothermia and normoglycemia[25].
Identifying these high risk patients at an early stage prior to the development of irreversible injury is essential so that evidence-based therapies such as intravenous or intra-arterial thrombolysis or even hemicraniectomy can be applied. Accurate prognostication may also identify patients in need of intensive monitoring and may guide rehabilitation strategies.

2. Project Description :

This project is divided in two parts:

In the first one, we aim to study the epidemiology of severely presenting strokes: we want to characterise better what defines a severely presenting stroke, in terms of demographical,

clinical, biological and radiological caracteristics. What kind of acute and subacute caracteristics are especially seen in patients presenting such a subtype of stroke.

In the second one, we aim to define the predictors (in the acute as well as subacute phase) of good recovery after stroke by means of the modified Rankin score (mRS) at 3 month after the event.

The overall aims of this project are to identify:

- Which stroke patients are at risk of developing a severely presenting stroke.
- The predictors of good outcome in these patients.

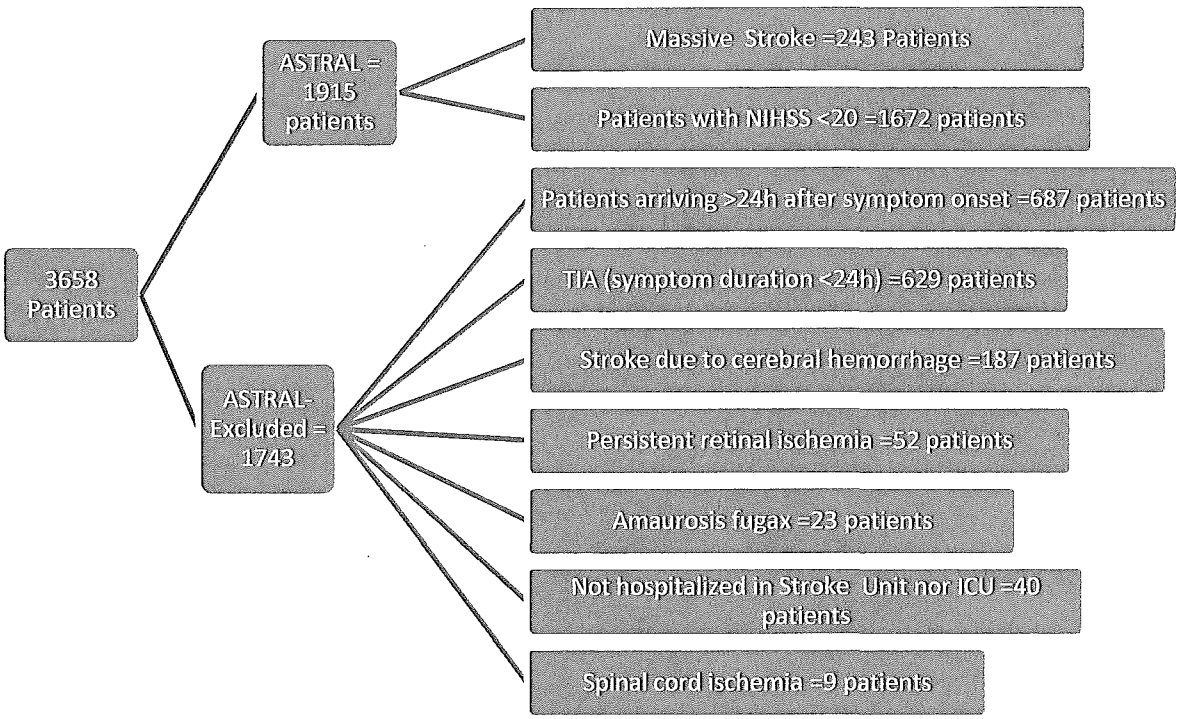
3. Methods

3.1 Patients

Inclusion criteria:
All consecutive patients with acute ischemic stroke admitted to the stroke unit and/or intensive care unit of the CHUV, which is a community hospital for a population of circa 350 000, as well as the only Stroke Unit for 720 000 persons, within 24hours from January 2003 to December 2010. Data of these patients were prospectively included in the Acute STroke Registry and Analysis of Lausanne (ASTRAL)[26]. The ethics commission for research on humans of the Canton of Vaud, subcommission III, has approved the scientific use of ASTRAL.

Exclusion criteria:
In ASTRAL: Patients with ischemic stroke whose last proof of good health was > 24 hours before hospital arrival, patients with haemorragic strokes (intracerebral hemorrhage, subarachnoid hemorrhage), and patients with transient ischemic attacks (TIA) as defined by complete remission of symptoms and signs within 24 hours were excluded.
In this project: For part 1, we included all ASTRAL patients, and for part 2, we excluded patients with a NIHSS score <20.

Fig 1: Identification



3.2 Stroke classification

The classification used in this registry is the TOAST (Trial of Org-10172 in Acute ischemic Stroke) classification [27] with some modifications according to recent progress of research in this field[28] :

1. Large artery atherosclerosis (ipsilateral stenosis of >50% or occlusion)
2. Likely atherothrombotic stroke
    - Ipsilateral internal carotid stenosis or another intra/extra cranial artery stenosis of < 50% or
    - Aortic arch plaques > 4 mm in thickness without a mobile component or
    - History of myocardial infarction or coronary recanalization or
    - At least two of the following:
        - Arterial hypertension or hypertensive retinopathy
        - Diabetes mellitus
        - Current smoking
        - Dyslipidemia
3. Cardioembolic stroke
4. Lacunar stroke
5. Arterial dissection
6. Acute stroke of other determined origin
7. Undetermined etiology
8. Coexisting and multiple causes
9. Stroke attributed to patent foramen ovale

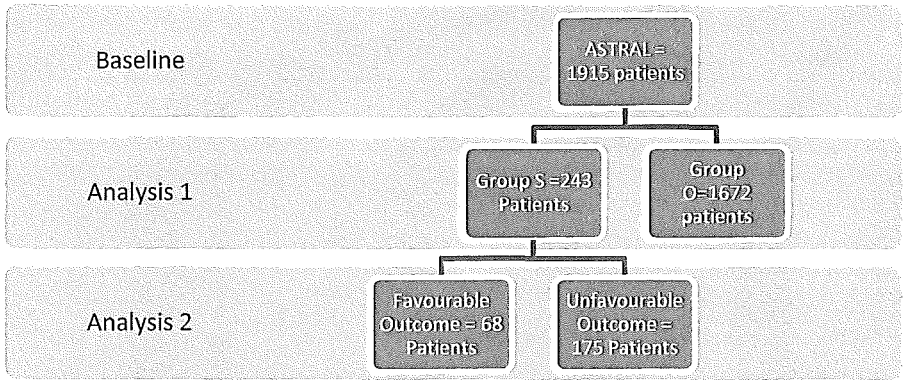
The NIHSS Scale

This score has been described by T. Brott in 1989[29] to evaluate the severity of ischemic stroke in the acute phase. It is very practical and widely used in both research and clinical practice and has been validated for both carotid and vertebro-basilar strokes. The average time spent to complete this evaluation is 6'30'', and the inter-observer reproducibility has been improved recently by an video e-learning program and international guidelines on the way one should perform the test[11].
The limitations of this scale include its significant interobserver variability and the modest correlation relation between stroke severity and the size of the infarct with some large strokes leading to only moderate NIHSS (eg. a complete infarct of the posterior cerebral artery gives a score of 10). Moreover, a given score may represent different clinical deficits, which may be associated with different prognosis (both a moderate central paresis of nerve VII and a severe aphasia correspond to a score of 2)
The sensitivity of this scale is limited by the number of items tested and by the low range of grades within the scale, but this limit aims to increase to inter-observer reproducibility, which is especially necessary for clinical trials. This lack of sensitivity has been criticised on the evaluation of clinical improvement or worsening of patients[29], except in minor strokes with no functional impairment, where functional scales are useless due to their threshold-effect. This is one of the reasons that we employ mRS in the second part of this project to assess patients' functional outcome in time. In this project, despite its known limitations in assessing different vascular territories, we used this scale with an arbitrary cut-off of 20 or above on admission to define severe strokes.

The modified Rankin Scale (mRS)

The **modified Rankin Scale** (mRS) is a commonly used scale for measuring the degree of disability or dependence in the everyday life of stroke patients, and it is widely used as a clinical outcome measure in stroke clinical trials. It was originally introduced in 1957 by Rankin. The first publication of the current modified Rankin Scale was in 1988 by van Swieten *et al.*, who also published the first interobserver agreement analysis of the modified Rankin Scale[30]. Interobserver reliability of mRS can be improved by using a structured questionnaire during the interview process[31] and by having raters undergo a multimedia training process[32]. In this project mRS was assessed by mRs-certified personnel at 3 months in the outpatient clinic. At 12 months, and for patients unable to attend the 3 month outpatient clinic, mRs was assessed by a structured telephone interview by mRs-certified personnel.

Fig. 2 : Project overview.



3.4 Other information collected

In addition to the above mentioned data, we collected detailed information in the following areas:

- Demographics (Patients' age, gender, ethnicity and insurance, pre-existing vascular risk factors, the mode of transport to CHUV)
- Cerebrovascular risk factors
- Previous clinical TIA, stroke or ocular ischemia
- Medication at the time of stroke onset
- Timing of onset of symptoms or last well time (if onset is unknown), time of arrival, time intervals from stroke onset to brain imaging, to intervention (if not contraindicated).
- Clinical symptoms and signs
- NIHSS on admission, 24 hours, and 7 days,
- modified Rankin scale before and 7 and 90 days after the stroke.
- Clinical follow up at 3 month (NIHSS and mRS) and 12month (mRS). The 3 months outcome data were collected either during follow-up consultation in person or by phone with the patients or relatives.
- Acute and subacute neuroimaging (parenchymal imaging within 6 hours after admission)
- Acute and subacute arterial imaging (mostly CT-angiography)
- Laboratory examinations
- Intervention details (thrombolysis, mechanical recanalisation, hemicraniectomy)

2.5 Statistical analysis

For the first part of this project, all ASTRAL patients are sepatated in two groups, where their NIHSS score at admission (NIHSSadm) is the dependent variable :

- Group S (Severe) includes patients with a severely presenting stroke with a NIHSSadm ≥ 20
- Group O (Other) includes patients with a NIHSSadm < 20

For the second part of this project, all patients from the « Severely presenting » Group (see part 1) will be sepatated in two groups, where their mRS score at 3 months (mRS 3m) is the

dependant variable : patients will be separated into a favourable (F) and a unfavourable (UF) outcome group.

Outcome	Modified Rankin Score	Definition
Favourable	0	No symptoms at all
	1	No significant disability despite symptoms; able to carry out all usual duties and activities
	2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
	3	Moderate disability; requiring some help, but able to walk without assistance
Unfavourable	4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
	5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
	6	Dead

We considered moderate disability in the independent group since we only included severe (NIHSS>20) patients in part 2 of the study. mRS score ≤ 3 is a common cut-off value in severe stroke such as haemorrhagic or posterior fossa stroke studies, and given the initially severe clinical picture making it a priori less probable to achieve a mRS of 0, 1 or 2.

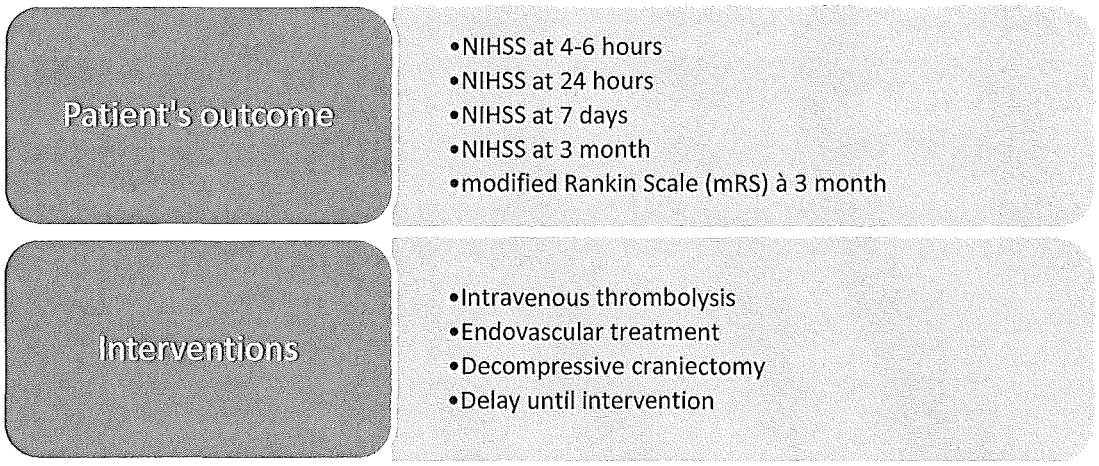
Part One: Comparison of characteristics and predictors of group S vs. group O after exclusion of patients according to ASTRAL requirements. A univariate analysis of the individual variables was conducted to assess differences between the two groups. For univariate comparison, we used the x^2 test for continuous data (unless distribution is not normal, where we used the Q-Q plot). For categorical data we used the Wilcoxon test.

Part Two: *Analysis of Outcome* : Within group S, we subdivided patients according to their outcome (favourable vs. unfavourable) at 3 months. We then compared the patients who had a favourable outcome despite the fact that they came in with a severe, severely presenting stroke. A univariate analysis of the individual variables was conducted to assess differences between the two groups. The variables which were significant in the univariate analysis ($p<0.1$, in order to decrease the risk of a type II error), were entered into a multiple logistic regression model to identify predictors favourable outcome in patients with severely presenting stroke. All analyses were conducted with the STATA 9.2 program.

Table A : variables included in the univariate analysis

Demographics	•Age •Sex •Insurance
TOAST	•Atherosclerosis •Lacunar •cardiac & Patent Foramen Ovale •Dissection •Unknown •Other/rare/multiple
Risk factors	•Hypertension •Diabetis •Cholesterol •Smoking •Atrial Fibrilation •CAD •Prosthetic mechanical valve •low (<35%) ejection fraction •old symptomatic stroke
Medication at admission	•Antiplattelets (Acetylsalycilate, Clopidogrel, Asasantin) •Anticoagulants (oral, hepar,Low-weight Heparin) •Antihypertensive •Hypolipemic •Antidiabetic (oral or insulin)
Metabolic and physiologic caracteristics	•Systolic blood pressure •Diastolic blood pressure •Heart rate •Body temperature •Glycemia •Creatinin •Cholesterol •Hemoglobinemia •Hematocrit •White Cell Count •Platelets count
parenchymal lesions (CT or MRI)	•acute lesions •chonic lesions
Arterial findings (CT or MRI)	•in ischemic territory (and ischemic terr. +other terr.) •in non-ischemic territory
Other factors	•pre-stroke mRS •Time of stroke onset

Table B: analysis of subacute variables (not included in multivariate model of part one).



4. Results

Part one: Defining the severely presenting stroke patients' profile.

1915 Severely presenting stroke patients's clinical and paraclinical characteristics are described in Table A. Median age was 68.8 years., the population consisted of 43.9% women. 243 patients (12.7%) belonged to the group S and 1672 (87.3%) in group O.

Table C : Results concerning the analysis of table A variables. (Univariate analysis)

Patients' caracteristics	All patients (n=1915)	Severely presenting Group patients (S)(n=243)	Others Group patients (O) (n=1672)	Odd Ratio (95% CI)	p-value
Demographics					
Age, mean (±SD)	68.80 (15.49)	69.63 (16.88)	68.68 (15.27)	1.004	0.37
Female Sex, n, (%)	840 (43.96)	130 (53.5)	710 (42.57)	0.644	<0.01
Insurance status n, (%)	1526 (80.36)	199 (82.57)	1327 (80.04)	0.846	0.35
Metabolics					
Systolic Blood Pressure (mmHg), mean (±SD)	158.87 (28.53)	156.44 (31.41)	159.22 (28.08)	0.996	0.16
Diastolic blood pressure, (mmHg), mean (±SD)	89.21 (17.82)	86.76 (20.91)	89.57 (17.30)	0.991	0.02
Heart Rate (min^{-1}), mean (±SD)	79.97 (18.05)	83.78 (22.34)	79.41 (17.27)	1.012	<0.01
Temperature (°C), mean (±SD)	36.39 (0.66)	36.26 (0.80)	36.41 (0.64)	0.703	<0.01
Glucose (mmol/l), mean (±SD)	7.17 (2.95)	7.55 (2.39)	7.11 (3.02)	1.038	0.05
Creatinine (mmol/l), mean (±SD)	96.75 (51.69)	93.26 (44.75)	97.27 (52.64)	0.998	0.27
Hemoglobin (g/l), mean (±SD)	138.77 (32.88)	132.86 (19.66)	139.65 (34.33)	0.981	<0.01
Hematocrit (%),mean (±SD)	41.05 (4.98)	39.97 (6.28)	41.21 (4.74)	0.950	<0.01
total cholesterol (mmol/l), mean (±SD)	5.59 (4.47)	5.59 (4.44)	5.59 (4.48)	1.000	0.98
White cell count (x103/l), mean (±SD)	8.65 (4.42)	9.83 (4.73)	8.48 (4.35)	1.064	<0.01

Platelets (x10³/l), mean (±SD)	231.53 (73.09)	232.70 (85.59)	231.35 (71.07)	1.000	0.79
Risk factors (pre-existing or newly discovered)					
Hypertension, n, %	1280 (66.91)	140 (57.85)	1140 (68.22)	0.639	<0.01
Diabetes mellitus, n, %	303 (15.91)	33 (13.75)	270 (16.22)	0.824	0.33
Active smoking, n, %	444 (23.53)	46 (19.83)	398 (24.05)	0.781	0.16
Atrial fibrillation, n, %	482 (25.21)	94 (38.84)	388 (23.23)	2.098	<0.01
Coronary heart disease, n, %	284 (14.85)	37 (15.23)	247 (14.79)	1.035	0.86
Prostetic valve, n %	59 (3.09)	9 (3.73)	50 (2.99)	1.257	0.53
Low ejection fraction (<35%), n, %	85 (4.56)	20 (8.62)	65 (3.99)	2.271	0.02
Previous cerebrovascular event (stroke, TIA or retinal), n, %	28 (1.47)	3 (1.23)	25 (1.5)	0.771	0.11
Medication at admission					
Aspirine, n, %	609 (32.12)	72 (30.13)	537 (32.41)	0.899	0.48
Antiplatelets(Clopidogrel&ASA&Asasantine), n, %	681 (35.92)	81 (33.89)	600 (36.21)	0.903	0.48
Anticoagulant, n, %	192 (10.16)	29 (12.13)	163 (9.87)	1.261	0.28
Antihypertensive, n, %	1045 (55.23)	123 (51.9)	922 (55.71)	0.858	0.27
Hypolipemic, n, %	438 (23.16)	41 (17.23)	397 (24.02)	0.658	0.02
Antidiabetics, n, %	155 (8.16)	14 (5.83)	141 (8.52)	0.665	0.16
Stroke mechanism					
Atherosclerosis (≥50% stenosis), n, %	254 (13.60)	30 (12.55)	224 (13.76)	0.900	0.61
Unknown or Atherosclerosis (<50%), n, %	458 (24.53)	50 (20.92)	408 (25.06)	0.915	0.72
Cardiac or PFO, n, %	617 (33.05)	118 (49.37)	499 (30.65)	1.766	0.01
Lacunar/microangiopathy, n, %	277 (14.84)	0 (0)	277 (17.01)		(not analysable)
Dissection, n, %	92 (4.93)	18 (7.53)	74 (4.75)	1.816	0.07
Other/rare, n, %	77 (4.12)	11 (4.60)	66 (4.05)	1.244	0.56
Multiple/coexisting, %	92 (4.93)	12 (5.02)	80 (4.91)	1.023	0.76
Radiological Findings (CT-Scan or MRI)					
Arterial findings in ischemic territory (stenosis>50% or occlusion), n, %	796 (49.91)	616 (88.24)	180 (44.28)	9.436	<0.01
Acute Parenchymal findings, n, %	632 (35.53)	149 (63.4)	483 (31.28)	3.806	<0.01
Chronic parenchymal findings, n, %	788 (47.21)	90 (40.18)	698 (48.3)	0.719	0.02
Old Strokes (radiologically), n, %	514 (30.80)	55 (24.55)	459 (31.76)	0.699	0.03
Leukoaraiosis, n, %	421 (25.22)	47 (20.98)	374 (25.88)	0.760	0.12
Event circumstances					
known, n, %	1074 (56.11)	126 (51.85)	948 (56.73)	0.821	0.15
approximative (+/- 1h), n, %	260 (13.58)	34 (13.99)	226 (13.52)	1.040	0.84
Unknown (>1h, but less than 24h, excluding wake-up strokes), n, %	97 (5.07)	32 (13.17)	65 (3.89)	3.747	<0.01
During night sleep, n, %	445 (23.25)	49 (20.16)	396 (23.70)	0.813	0.22
During day sleep, n, %	38 (1.99)	2 (0.82)	36 (2.15)	0.377	0.18
pre-stroke modified Rankin Scale, mean, (±SD)	0.69 (1.00)	0.85 (1.17)	0.67 (0.97)	1.178	0.01

The univariate comparison between the two groups showed significant differences between the two groups for certain variables listed by category below :

Epidemiology : Patients in the severely presenting group are more likely to be females (53.50%).

Acute metabolic and physiologic values : Severely presenting stroke patients have a higher heart rate and WCC at admission, but acute diastolic blood pressure, body temperature, hemoglobin and hematocrit were significantly lower in the severely presenting stroke group.

Risk factors and medication : Hypertension was less frequent in group S, but atrial fibrillation and heart failure (low ejection fraction) was more common. At admission severely presenting stroke patients are less frequently under hypolipemic treatment.

Stroke mechanism : a higher percentage of dissection and cardiac etiology are leading to a severely presenting stroke. 15% of the patients in the « others » group had a lacunar etiology to their stroke, yet not a single stroke in the severely presenting group had this etiology.

Radiology: Occlusion or stenosis of the cervical/cerebral vessels are more frequent in the severely presenting group. Moreover, imaging studies analysis showed that these patients have less old ischemic lesions and leukoaraiosis than non-severely presenting stroke patients.

Stroke circumstances : For most of the patients, the exact time of stroke onset is known, but the proportion of unknown symptoms onset is significantly more frequent in severely presenting stroke patients (13% in the severely presenting group vs 5% in the others group).

Pre-stroke conditions : pre-stroke Independence measured by mRS was higher in the severely presenting stroke patient population than in the others stroke patient population.

The results of the univariate analysis of variables in Table B **not** included in the multivariate analysis are listed in the Table D :

Table D : of the univariate analysis of variables in Table B (not included in the multivariate analysis)

Patients' caracteristics	All Patients (n=1915)	Group S (n=243)	Group O (n=1672)	Odd Ratio (95%CI)	p-value
Stroke severity					
Pre-stroke NIHSS, mean, (±SD)	0.51 (1.46)	0.83 (1.99)	0.47 (1.38)	1.132	0.03
NIHSS at 4h-6h, mean (±SD)	8.19 (7.58)	22.81 (5.91)	6.08 (5.04)	1.556	<0.01
NIHSS at 24h, mean (±SD)	7.65 (8.07)	22.07 (8.06)	5.55 (5.52)	1.318	<0.01
NIHSS at 7 days, mean (±SD)	6.92 (9.99)	23.13 (12.81)	4.59 (6.88)	1.16	<0.01
Interventions					
I.V. Thrombolysis, n, %	302 (15.79)	72 (29.63)	230 (13.78)	2.726	<0.01
Endovascular thrombolysis, n %	16 (0.84)	7 (2.88)	9 (0.54)	6.772	<0.01
Delay between admission and intervention, mean, (±SD)	80.83 (115.37)	91.61 (152.10)	77.41 (101.06)	1.001	0.32
Craniectomy , n, %	0.78	3.70	0.36	10.667	<0.01
Patients' Outcome					
modfied Rankin Scale at 3 months, mean, (±SD)	2.33 (1.96)	4.55 (1.75)	1.99 (1.76)	1.881	<0.01

Interventions and acute patient management: In univariate comparison, severely presenting stroke patients undergo more frequentely an invasive treatment such as intravenous or endovascular thrombolysis, or hemicraniectomy than the others. On the contrary, time from arrival at hospital to treatment (so-called « door-to-needle time ») of a group S patient is 15' longer compared to patients with a group O patient.

Stroke severity and outcome : Both severely presenting (S) and other strokes (O) patients had a NIHSS which decreased gradually within the first 24hours, nevertheless, their evolution in the sub-acute phase was very different : between 24h and 7days, Group S patients showed a slight but steady increase of their NIHSS. On the contrary, group O patients evolved with a further reduction of the NIHSS score. As expected, the mRS score at 3 month was significantly higher in patients within group S (median : 4-5) than patients in group O (median : 2).

Results of Multivariate analysis (extracted from significant values in Table C) are presented in Table E:

Table E: multivariate analysis of predictors of severely presenting strokes.

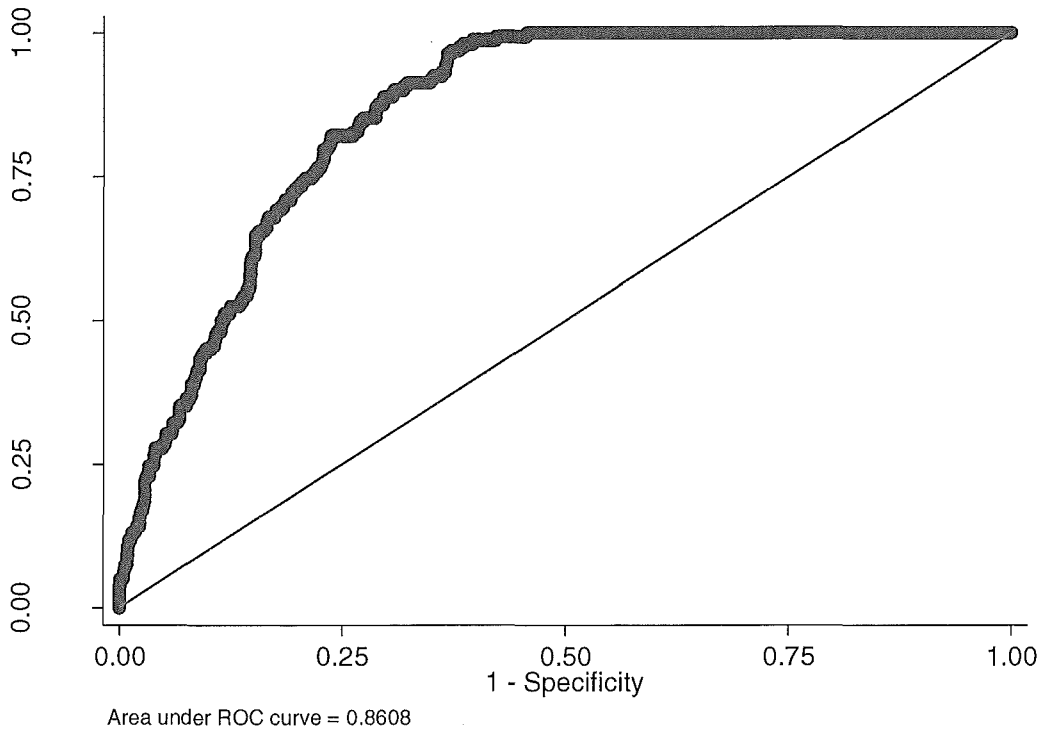
Patients' caracteristics	Odd Ratio (95% CI)	p-value
Metabolics		
Hemoglobin	0.976, (0.965 - 0.987)	<0.01
White cell count	1.054, (1.001 - 1.109)	0.04
Stroke Mechanisms		
Cardio-embolic	1.744, (1.193 - 2.548)	<0.01
Radiological Findings (CT-Scan or MRI)		
Arterial findings in ischemic territory (stenosis>50% or occlusion)	0.037, (0.0158 - 0.0862)	<0.01
Any Acute Parenchymal Finding , (Leukoaraiosis, non vascular lesion, old stroke, other lesion)	2.655, (1.795 - 3.924)	<0.01
Old Strokes (radiologically)	0.431, (0.258 - 0.719)	<0.01
Event circumstances		
Unknown (>1h, but less than 24h, excluding wake-up strokes)	2.351, (1.143 - 4.831)	0.02
pre-stroke modified Rankin Scale)	1.279, (1.041 - 1.569)	0.02

Among the 1917 patients with acute ischemic stroke included in this study, the multivariate analysis allows us to adjust for confounding factors when describing the severely presenting stroke population. According to our analysis, these patients have a higher pre-stroke mRS, lower haemoglobin, and a higher white cell count. Radiologically, they show less frequently old stroke lesions, more acute parenchymal findings and more arterial anomalies within the ischemic territory. Concerning the etiology, the cardioembolic and the arterial dissection were more frequent mechanisms in Group S compared to group O. Finally, we also observed that

the exact onset time of the stroke was less frequently known in the severely presenting stroke group.

In order to assess the performance of our multivariate analysis, figure 3 presents the ROC curve, which shows that our model has an area under the curve of around 86%, which reflects that it is a good predictor of the patients' situation.

Fig. 3 : ROC curve.



Part two: Predictors of good outcome in severely presenting stroke patients.

In this part, we studied first (Tables F and G) the acute phase predictors of favorable outcome at three months within group S, including acute recanalisation treatments. This is to show which characteristics of stroke patients at the emergency ward will lead them to good outcome. We then added predictors collected in the subacute phase (24-48 hours after stroke), including subacute NIHSS values, metabolic values, recanalisation on repeat arterial imaging, and parenchymal findings in subacute neuroimaging. This is to see if we can better predict a patient's outcome once he is a the neurology ward.

Table F : Univariate analysis of acute phase predictors of favourable outcome in group S patients.

Patient's caracteristics	All patients	Favourable outcome (mRS 0-3 at 3 months)	Unfavourable outcome (mRS 4-6 at 3 months)	Odds Ratio	p-value
(N)%	243	(68) 28%	(175)72%		

Demographics					
Age mean,(±SD)	69.63 (16.88)	61.45 (16.19)	72.80 (16.10)	0.960	<0.01
Female Sex, n, %		30 (44.12)	100 (57.14)	1.680	0.07
Private Insurance, n, %		17 (25.00)	25 (14.45)	1.973	0.06
Metabolic & Physiologic					
Systolic blood pressure (mmHg) mean,(±SD)	156.44 (31.41)	149.41(28.71)	159.19 (32.06)	0.989	0.03
Diastolic blood pressure (mmHg) mean,(±SD)	86.76 (20.91)	83.46(16.95)	88.05 (22.17)	0.989	0.13
Heart rate (min-1) mean,(±SD)	83.78 (22.34)	80.87 (18.98)	84.92 (23.48)	0.991	0.21
Temperature (°C) mean,(±SD)	36.26 (0.80)	36.07 (0.63)	36.33(0.84)	0.632	0.02
Glucose (mmol/l) mean,(±SD)	7.55 (2.39)	6.85(1.88)	7.82(2.51)	0.811	0.01
Serum creatinine (mmol/l) mean,(±SD)	93.26 (44.75)	84.21 (23.59)	96.72(50.17)	0.988	0.03
Hemoglobine (g/l) mean,(±SD)	132.86 (19.66)	133.70 (21.29)	132.54(19.06)	1.003	0.68
Hematocrit mean,(±SD)	39.97 (6.28)	39.92(5.66)	39.98 (6.52)	0.998	0.95
Total cholesterol (mmol/l) mean,(±SD)	5.59 (4.44)	5.08(1.55)	5.77 (5.09)	0.943	0.37
White blood cell count (x103/l) mean,(±SD)	9.83 (4.73)	9.93 (4.77)	9.79 (4.72)	1.006	0.84
Platelet count (x103/l) mean,(±SD)	232.70 (85.59)	233.85 (73.58)	232.26 (89.97)	1.000	0.90
Risk factors (new or newly discovered)					
Hypertension,n, %	140, (57.85)	32 (47.06)	174 (62.07)	0.543	0.04
Diabetes mellitus,n, %	33, (13.75)	10 (14.71)	23 (13.37)	1.116	0.79
Smoking,n, %	46, (19.83)	17 (25.76)	29 (17.47)	1.638	0.16
Atrial fibrillation,n, %	94, (38.84)	18 (26.47)	76 (43.68)	0.464	0.02
CAD,n, %	37, (15.23)	13 819.12)	24 (13.71)	1.487	0.30
Mechanic Valves,n, %	9, (3.73)	2 (2.99)	7 (84.02)	0.734	0.70
Low Ejection Fraction (<35%),n, %	20, (8.62)	5 (7.69)	15 (88.98)	0.844	0.75
Patient's History					
Previous cerebrovascular event (AVC, AIT or retinal ischemia) ,n, %	187, (78.24)	58 (87.88)	129 (74.57)	2.53	0.03
Medication at admission					
Anticoagulant,n, %	29, (12.13)	10 (14.93)	19 (11.05)	1.412	0.41
Both ASA & Anticoag,n, %.	81, (33.89)	15 (22.39)	66 (38.37)	0.463	0.02
Antihypertensive treatement, n, %	123, (51.90)	33 (50.00)	90 (52.63)	0.900	0.72
Hypolipemic, n, %	41, (17.23)	15 (22.73)	26 (15.12)	1.651	0.17
Antidiabetics, n, %	14, (5.83)	5 (7.46)	9 (5.20)	1.469	0.51
TOASTMechanism					
Atherosclerosis (>=50% stenosis), n %	30, (12.55)	6 (8.96)	24 (13.95)	0.607	0.30
Unknown Or atherosclerosis <50%, n, %	50, (20.92)	14 (20.90)	36 (20.93)	0.998	1.00
Cardiac Or PFO, n, %	118, (49.37)	30 (44.78)	88 (51.16)	0.774	0.38
Lacunar/ microangiopathy, n, %		0	0		
Dissection, n, %	18, (7.53)	9 (13.43)	9 (5.23)	2.810	0.04
Other/rare, n, %	11, (4.60)	7 (10.45)	11 (2.33)	4.900	0.01
Multiple/coexisting, n, %	12, (5.02)	1 (1.49)	11 (6.40)	0.222	0.15
Arterial anomalies (on CT, if no CT performed, checked on MRI or Doppler:					
Arterial findings in ischemic territory , n, %	180, (88.24)	56 (90.32)	124 (87.32)	1.35	0.54
Parenchymal findings (on CT; if no CT performed, checked on IRM :					

Any Acute Parenchymal Finding , (Leukoaraiosis, non vascular lesion, old stroke, other lesion), n, %	90, (40.18)	17 (28.33)	73 (44.51)	0.684	0.20
Chronic parenchymal findings (leukoaraiosis & other), , n, %	86, (38.39)	17 (28.33)	73 (44.51)	0.544	0.06
Old Strokes, n, %	55, (24.55)	13 (21.67)	42 825.61)	0.803	0.54
Leukoaraiosis, n, %	47, (20.98)	7 (11.67)	40 (24.39)	0.409	0.04
Acute imaging description					
**Any acute finding (Acute stroke, Asymptomatic mass, Hemorragic transformation) n, %	149, (63.40)	37 (56.92)	112 (65.88)	0.684	0.20
Timing of Onset					
Known ,n, %	126, (51.85)	44 (64.71)	82 (46.86)	2.079	0.01
Approx,n, %	34, (13.99)	4 (5.88)	30 (17.14)	0.302	0.03
During night sleep,n, %	49, (20.16)	12 (17.65)	37 (21.14)	0.799	0.54
Unknown (>1h but less than 24h) ,n, %	32, (13.17)	7 (10.29)	25 (14.29)	0.688	0.41
During day sleep,n, %	2, (0.82)	1 (1.47)	1 (0.57)	2.596	0.50
Pre-clinical status					
**Pre-stroke NIHSS mean,(±SD)	0.83, (1.99)	0.88(2.64)	0.81(1.70)	1.017	0.89
mRSPreHosp mean,(±SD)	0.85,(1.17)	0.41(0.81)	1.02(1.24)	0.558	<0.01
Interventions					
IV-standard,n, %	72, (29.63)	32 (47.06)	40 (22.86)	3.300	<0.01
IA-standard,n, %	7, (2.88)	3 (5.88)	3 (1.71)	5.500	0.03
IV or IA,n, %	79, (32.51)	36 (52.94)	43 (24.57)	3.453	<0.01
Craniectomy,n, %	9, (3.70)	3 (4.41)	6 (3.43)	1.300	0.72
**Timing of Intervention mean (per min.),(±SD) ,n, %	152.1, (91.61)	13.41(4.93)	13.00 (5.48)	1.000	0.39

**: not included in multivariate model.

Epidemiology : Age difference between the two groups is significant (61.45% vs 72.80%), which means that the older patients within group S have less chance to be independent at three months. Insurance status hasn't shown to be significant (OR : 1.97/p-val : 0.06) but there is a trend that seems to favor private patients.

Acute metabolic and physiologic values : The only metabolic value at the emergency room that seems to influence outcome in stroke patients is glucose, as admission hyperglycemia was significantly associated with unfavourable outcome in the severely presenting stroke population.

Timing of Onset: Known onset was significantly associated with favourable outcome in patients with severely presenting stroke.

Pre-clinical status: pre-stroke functional status measured by mRS was significantly higher in unfavourable outcome severely presenting stroke patients.

Interventions : Invasive treatement is efficient when applied according to ESO guidelines, as significantly more severely presenting stroke patients have a good outcome when they underwent I.V. thrombolysis or I.V. & I.A. thrombolysis together. I.A. intervention doesn't seem to influence the outcome so strongly (OR :5.5/ p-value : 0.03), but numbers are low.

In multivariate analysis of the acute phase (table G), favourable outcome was predicted by lower age and lower initial temperature. Private insurance status, lower pre-existing functional handicap, lower glycaemia and undertaking of recanalisation treatment also increased the probability of favourable outcome. If subacute variables were added in the multivariate analysis (table I), treatment with hypolipemic agents (mostly statins) increased the probability of favourable outcome. The pre-existing functional handicap was replaced by past cerebrovascular events, acute by subacute (24-48 hour) glycaemia, and recanalisation treatment by (therapeutic or spontaneous) recanalisation. The ROC-AUC for predicting favourable outcome after severe stroke using the acute variables was 82%, and 81% when adding the subacute variables.

Table G: Multivariate analysis of acute phase predictors of favourable outcome in patients with initially severely presenting stroke.

Patient's caracteristics	Odd Ratio (95% CI)	p-value
Pre-stroke status		
Pre-stroke mRS	0.622, (0.405 - 0.954)	0.03
Demographics		
Age	0.952, (0.929 - 0.975)	<0.01
Private Insurance	2.517, (1.058 - 5.988)	' ??
Metabolics		
Acute Temperature(°)	0.423, (0.239 - 0.745)	<0.01
Acute Glucose	0.746, (0.612 - 0.908)	<0.01
Intervention		
Intervention (I.V. or I.A.)	2.476, (1.207 - 5.081)	0.01

ROC Curve:

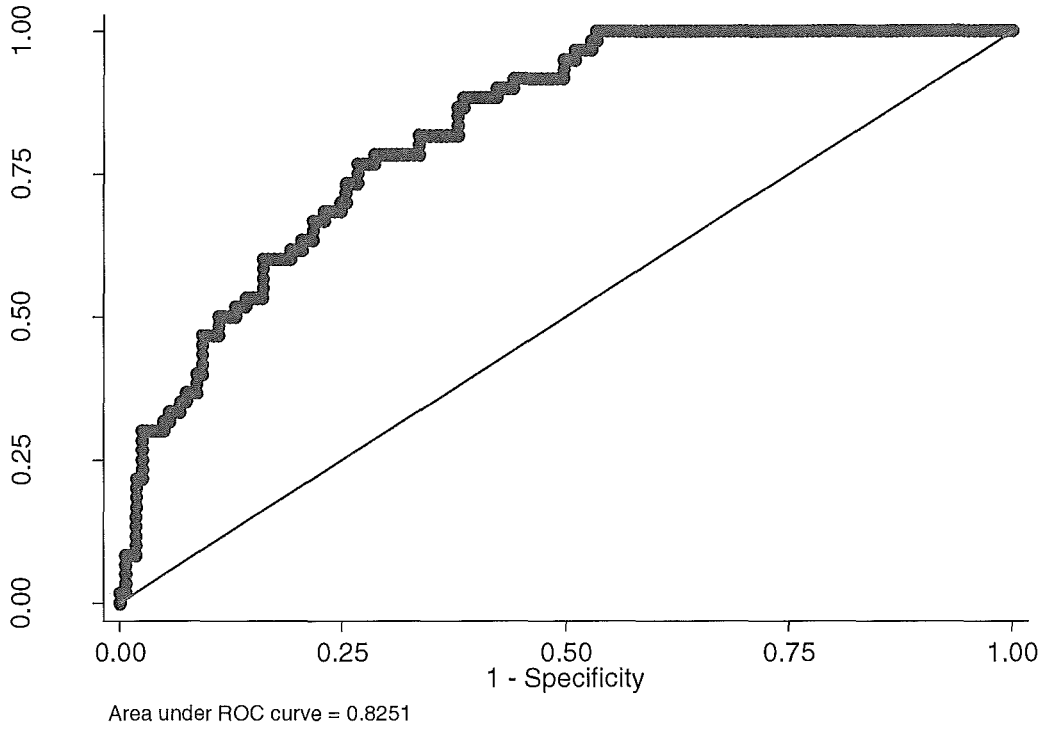


Table H: Univariate analysis of subacute predictors of favourable outcome in patients with initially severely presenting stroke

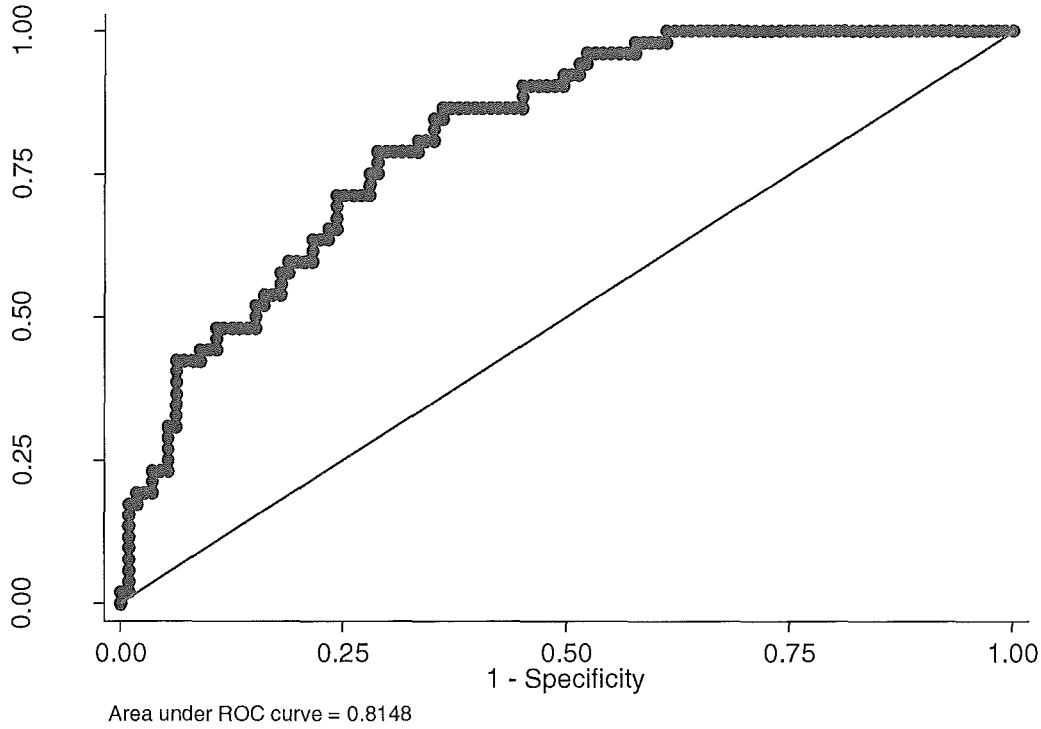
Patient's caracteristics	All patients	Favourable outcome (mRS 0-3 at 3 months	Unfavourable outcome (mRS 4-6 at 3 months))	Odds Ratio	p-value
N (%)	243 (100%)	69 (28%)	174 (72%)		
Subacute metabolic values					
Systolic blood pressure (mmHg) mean,(±SD)	143.47 (21.93)	139.78 (21.90)	145.07 (21.81)	0.989	0.1
Diastolic blood pressure (mmHg) mean,(±SD)	68.70 (15.63)	67.55 (15.78)	69.19 (15.59)	0.993	0.472
Heart rate (min-1) mean,(±SD)	82.55 (18.32)	76.25 (16.68)	85.26 (18.38)	0.970	<0.01
Temperature (°C) mean,(±SD)	37.01 (0.70)	36.89 (0.74)	37.06 (0.68)	0.694	<0.01
Glucose (mmol/l) mean,(±SD)	6.41 (1.93)	5.93 (1.24)	6.65 (2.16)	0.772	0.02
Serum creatinine (mmol/l) mean,(±SD)	89.53 (71.77)	79.19 (25.44)	93.48 (82.67)	0.990	0.16
Hemoglobine (g/l) mean,(±SD)	126.59 (19.56)	124.48 (20.79)	127.53 (19.03)	0.992	0.4
Hematocrit mean,(±SD)	38.04 (5.38)	37.19 (5.32)	38.41 (5.39)	0.958	0.22
Total cholesterol (mmol/l) mean,(±SD)	8.12 (9.37)	4.84 (1.06)	9.76 (11.22)	0.904	0.35
White blood cell count (x103/l) mean,(±SD)	11.21 (3.91)	10.69 (3.33)	11.45 (4.13)	0.948	0.29
Platelet count (x103/l) mean,(±SD)	215.95 (74.33)	218.71 (67.46)	214.71 (77.52)	1.00	0.77
Subacute imaging findings					
Any finding (acute stroke, HT, mass effect, other) , n, %	150, (96.15)	51 (92.73)	99 (98.02)	0.257	0.13
Subacute vascular imaging					
Significant Pathology in non-isch territory or none, n, %	38, (32.76)	18 (40.00)	20 (28.17)	1.7	0.19
Atheromatose :yes, n, %	33, (57.89)	9(42.86)	24(66.67)	0.375	0.08
Recanalisation					
Overall Complete, n, %	26, (11.16)	18 (26.47)	8 (4.85)	7	<0.01
Overall improvement, n, %	40, (17.17)	17 (25.00)	23 (13.94)	2.05	0.04

Overall not, n, %	67, (28.76)	15 (22.06)	52 (31.52)	0.615	0.15
Overall don't know/not checked, n, %	71, (30.47)	10 (14.71)	61 (36.97)	0.293	<0.01
Overall occlusion or stenosis in ischemic terr. never seen/documented, n, %	29,(12.45)	8 (11.76)	21 (12.73)	0.914	0.84
Overall : yes (complete, partial, improvement) , n, %	66, (28.33)	35 (51.47)	31 (18.79)	4.58	<0.01
excracranial Recanalisation :yes (complete, improvement) , n, %	20, (8.55)	6 (8.82)	14 (8.43)	1.05	0.92
intracranial Recanalisation : yes(complete, improvement , n, %	63, (27.16)	37 (54.41)	26 (15.85)	6.33	<0.01
Worstening of arterial patency (no, don't know, not documented) , n, %	225, (96.57)	65 (95.59)	160 (96.97)	1.47	0.6
Subacute NIHSS values					
****NIHSS at 24h (or change score or CoVariance between NIHSS adm and NIHSS 24h), mean,(±SD)**	22.07, (8.06)	15.13 (7.79)	24.67 (6.47)	0.807	<0.01
****NIHSS at 7 days (or change score or CoVariance between NIHSS adm at NIHSS 7d), mean,(±SD)**	23.13, (12.81)	12.01 (8.31)	27.56 (11.55)	0.852	<0.01
Orientation					
Death, n, %	84, (36.52)	0(0)	84(50.91)	Not calculable	
Home or short stay, n, %	11, (4.78)	9(13.85)	2(1.21)	13	<0.01
Long term institution, n, %	14, (6.09)	0(0)	14(8.48)	Not calculable	
Other acute care hosp, n, %	41, (17.83)	19(29.23)	22(13.33)	2.68	<0.01
rehabilitation, n, %	80, (34.78)	37(56.92)	43(26.06)	3.74	<0.01

Table I: Multivariate analysis of acute and subacute predictors of favourable outcome in patients with initially severe stroke.

Patient's caracteristics	Odd Ratio (95% CI)	p-value
Patient's history		
Previous cerebrovascular event (Stroke, TIA, retinalischemia)	3.00, (1.009 - 8.964)	0.04
Patient management		
Hypolipemic treatement	3.82, (1.341 - 10.895)	0.01
Metabolics		
Acute Temperature(°)	0.427, (0.232 - 0.785)	<0.01
Subacute Glucose	0.739, (0.565 - 0.966)	0.02
Demographics		
Age	0.943, (0.917 - 0.971)	<0.01
Arterial imaging		
Overall recanalisation	4.51, (1.957 - 10.407)	<0.01

ROC curve:



5. Conclusion & Discussion

Since severely presenting stroke is a dangerous and disabling condition, it is of prime importance to have a sensitive screening profile of the patients with suspicion of severely presenting stroke.

Analysis 1: Profile of Severely presenting stroke patients.

In the first part of this project, we were interested in defining the profile of patients that suffer a severely presenting stroke.
Previous studies[33, 34] have shown that young patients are more at risk to develop a severely presenting stroke with a mass effect. However, the results from our work didn't show any association between age and the characteristics of severely presenting strokes, despite the fact that age distribution was similar across all stroke types.
There was significantly more women in the severely presenting stroke group in the univariate analysis, which confirms a recent report [19]. In our population, gender did disappear during in the multivariate analysis, showing that this previous idea was not significant. Sex is hence a bad predictor of stroke severity. Similarly, pre-existing hypertension and pretreatment with hypolipemic agents were negatively associated with severe stroke in the univariate, but not in the multivariate analysis.
Our study helps evaluate which stroke etiology is the most frequent in patients with a severely presenting stroke. We showed that patients with an arterio-embolic stroke mechanism are at less risk to develop a severely presenting stroke. This can partially be explained by the fact that atherosclerosis is a chronic disease that evolves over decades, thus allowing collateral vascularisation to develop and potentially compensate for the vessel occlusion up to a certain

degree[33, 35] These results are congruent with data recently shown by our group regarding patient's outcome after proximal MCA occlusion[36]

Moreover, we see in this study that no severely presenting stroke was caused by microangiopathy. Understandably, by definition[25, 37] lacunar strokes don't cause the ischemia of a whole vascular territory.

Third, the cardio-embolic origin of stroke was significantly more frequent in patients with a severely presenting stroke, as also shown by previous studies[38, 39]

Finally, dissection is a known cause of severely presenting strokes (7.5% of dissections lead to group S, and 4.7% lead to group O). The large blood supply by the extracranial vessels explain the important ischemia induced by their occlusion[40].

Radiological data (mostly CT and CTAngio) revealed that both parenchymal and arterial findings in the ischemic territory are significantly more frequent in patients with a severely presenting stroke. This seems counterintuitive given that functional compensation for cerebral damage depends partially on the remaining "healthy" brain. However, patients who have less severe strokes might have a higher likelihood of having survived other minor strokes in the past. In addition, such survivors of previous strokes may receive better secondary prevention treatments, which have been shown to not only decrease recurrence, but also the severity of recurrent strokes.
The high prestroke mRS is leading to more risk belonging to group S. This shows that patients already disabled after a first event have less ability to compensate for new deficits.

Eventually, the exact time onset of the stroke is more often unknown in group S. The inability of the patient to express himself or to remember the early symptoms is probably the reason of this finding. The reason that this is not the case for sleep-onset stroke may be that such strokes are more frequently lacunar.
Severely presenting strokes more often received an intervention, such as thrombolysis or hemicraniectomy. This result seems reasonable, because the group was defined on clinical status of the patient, and the indication of thrombolysis as well. We also know that mass effect risk is higher in the severely presenting stroke type of patients [42, 43] which explains more surgical intervention.
Severe strokes were more frequent in patients with lower haemoglobin levels, suggesting that decreased oxygen transport capacity may increase infarct size.
White cell count has previously been associated with more severe clinical presentation and with worse early stroke outcome. It is not clear whether this is a direct effect of white cell activity and inflammation in the lesioned brain, or whether it is rather a marker of associated conditions (e.g. fever, early infection, stress response) that may increase stroke severity and worsen outcome.
The NIHSS score, assessed at different times during hospitalisation, didn t evolve similarly between the two groups: In group A, NIHSS follows a decreasing pattern , which is not the case for group S, where the NIHSS increases again between 24hours and 7 days. This result is probably due to the clinical complications shown by severely presenting stroke patients, such as brain edema and hemorragic transformation[4, 33, 42, 43].
Regarding HT according to ECASS-2 definition, unfavourable outcome was associated with greater HT. However, the rate of hemorragic transformation cannot really be judged since it concerned only 3 out of the 243 patients in the acute phase.

In this study, the NIHSS at admission value was used as a dependent variable, it is why it is very interesting and important to study how this time point will have an influence on the evolution of the patient's affection. In analysing the mRS at 3month, we saw that 28% of the patients have a good outcome (mRS between 0 and 3 at 3 months). Previous studies had already shown certain predictors of good outcome in stroke patients, but not precisely in severely presenting stroke patients. This is why we performed analysis two, whose results are now discussed.

Analysis 2 : Good outcome in severely presenting stroke patients : acute and subacute predictors.

Severely presenting stroke patients are a specific type of patients, as we saw in the first part of this project. Few of them show a positive evolution of their neurologic situation (28%) and these patients are of main interest because they can lead us towards a better management of severe stroke patients in the acute phase as well as in the subacute phase, by identifying whether there are factors that can be modified in their profile, or if their evolution is mainly defined by their constitutional or demographic characteristics.
In the acute phase alone, the fact that increased age predicts significantly unfavorable outcome in group S patients. This situation can be attributed to two factors : on one side, the vulnerability of old patients when it comes to lesion size tolerance : reduction of the number of synapses in old age [44], diminished volume of cortical grey matter [45] and thus neuronal plasticity, which is diminished in old patients, and on the other side their ability to improve as much as young patients [46] in the rehabilitation period, which is also reduced.

Private insurance status – probably indicating a higher socioeconomic status – has previously been show to predict favourable outcome in stroke patients[47]. The reasons for this observation are not certain, although one of our previous studies showed lower initial stroke severity in privately insured patients; this was not confirmed in the current dichotomised study.

One last characteristic is a significant predictor in the multivariate analysis: temperature. Increased temperature at admission is associated with less favorable outcome at 3months, implying that tight monitoring of temperature from admission to the ward is important. Understandably less inflammatory conditions benefit towards a better patient prognosis. Febrile patients also might have other comorbidities influencing the outcome. This effect can also be understood by the fact that severely presenting stroke patients very often suffer dysphagia in the acute phase, leading to broncho-aspiration and further fever and pneumonia, the main complication after stroke[48] which has been shown to influence outcome of stroke patients[49]. The fact that hyperglycemia was correlated with unfavorable outcome at 3 months was also to be expected. We already knew that the glycemia in the acute phase influenced stroke patients prognosis [50] so this finding confirms the same situation for severe stroke patients.

Interestingly, stroke etiology doesn't show to be significant in the model; this could be due to the fact that as we already saw in part one, there were no lacunar strokes in the severely presenting stroke group, so this was a more or less a homogenous group regarding outcome. It also shows that in severe strokes, the probablility to find an occlusion is very high, which probably explains that the outcome is more dependent on the patients's vascular status than the stroke's etiology. This is also probably the reason why this type of patients benefit from thrombolysis.

Another reason why severely presenting stroke patients have a better outcome when thrombolysed might be patient selection : regarding state-of-the-art thrombolysis, patients with a hypodensity of >50% of the middle cerebral artery are excluded for intervention, so the lesion size might be artificially smaller in those patients. (a territory >50% of the cerebellum is also an exclusion criterium, but that doesn't influence NIHSS as much) This finding at least confirms the benefit of thromblysis regardless of the stroke severity. In severe strokes, most patients have large occluding thrombi in intracranial arteries, which may need endovascular treatment for effective recanalisation; although only few of our patients underwent such treatments, an effective recanalisation strategy should be offered to severe stroke patient, particularly if the relationship between viable brain tissue and core is favourable.

Obviously patients with a higher pre-stroke mRS will have a higher post-stroke mRS at 3months, regardless of other factors, as the multivariate analysis showed.
Studying the dynamics of prognostic factors in severely presenting stroke, our study showed that the subacute phase seems very important when considering independence as outcome : acute temperature is still a value influencing patients' outcome regardless of when the assessement is done, and subacute glucose value is shown to be of main interest, since the results of our study seems to emphasize the management of hyperglycemia after 24h, once the patient is out of the emergency room. Hypergylcemic, not only diabetic patients, have a worse stroke outcome, since values >7.3 mmol/L are already associated with poor outcome[50], we show here the same effect in the subacute phase. Thus, establishing guidelines in stroke units regarding aggressive i.v insulinotherapy already when glycemia exceeds this value and defining the transition from i.v. to subcutaneous insulin treatement, is recommended after what we have shown here. Age is retrieved in our subacute analysis of prediction factors, meaning that it is a determinant composant of good outcome in severely presenting stroke patients.
Adding covariates from the subacute phase, we found previous clinical cerebrovascular events (stroke, TIA, retinal ischaemia) were independently associated with favourable outcome at three months. This was not explained by stroke mechanism but could indicate that patients who recovered from a previous stroke (rather than died) also have a better chance of recovery from a subsequent severe stroke; part of this may be due to genetics of neurovascular factors, anatomy of the cervico-cerebral vasculature including collaterals, or to ischaemic preconditioning[41]
Hypolipemic treatement : Even though this variable wasn't significant in the univariate analysis, in the mixed multivariate analysis for acute & subacute predictors, it was an independent predictor. This may be explained by pleiotropic effects of statins, especially on the cerebral vasculature.
The overall recanalisation of occluded arteries is shown in the mixed multivariate analysis to be significant and this confirms the benefit maintaining permerability of cerebral vessels, regardless of the subacute characteristics of the patient[51], if the aim is to have a better independance of the patient at 3months.

5. Conclusion

The analysis of the above mentioned factors has allowed to better understanding of risk factors, pathogenesis, and clinico-radiological patterns in patients with severely presenting stroke. It has therefore the potential to propose better preventive measures and appropriate treatment options.
Our results show that pre-stroke caracteristics of the patient, stroke etiology, hematological values of the patient, and acute radiological findings, influence the risk to develop a severely presenting stroke. Although some of the results were expected, some are unconsistent with previous work on the topic, such as decrease of hemoglobin, absence of chronic brain lesions or old strokes, and the absence of influence of age and blood pressure. The clinical evolution of these patients was significantly worse, despite the increased frequency of interventions. When analysing severely presenting strokes outcome in the severely presenting stroke group, it helped us understand whether the patient's neurological evolution when having a severely presenting stroke was to be influenced by its management in the emergency room, in the radiology lab or at the ward regarding the subacute period. Our work confirms a recent study showing that acute patient management in the subacute phase influences tightly outcome after stroke[52], which is shown by the fact that we find in the multivariate analysis characteristics that can be influenced by acute and subacute treatement, and secondary prevention, such as acute temperature, Glucose levels in the acute and subacute phases, hypolipemic medication, emergency treatement such like thrombolysis, and its success as vessel recanalisation.

Despite the fact that the subgroup of severely presenting strokes were destined to have a bad outcome, nevertheless, some have a good outcome and it is our work as clinicians to target them quickly, to manage them with the most appropriate therapy and to follow them thightly at the ward, and this is the only manner to give them a chance of independence in the post-stroke period.
This confirms the fact that acute ischemic stroke patients have to be taken care of in a Stroke Unit, and that Stroke has to be considered as an emergency like myocardial infarction.

Limitations of our work are the following:

One limitation of our work is its observational, single centre design. Furthermore, we did not include detailed analysis of perfusion imaging studies nor of collaterals in our analysis even though such factors were shown to be linked to outcome prediction in stroke patients[53]. The fact that only a few patients had endovascular treatment limited the ability to explore its effects; recanalisation (spontaneous or thrombolysis related) was frequently measured, however, and showed significant associations
with favourable outcome. We also accept that the NIHSS criterion of 20 and above causes slight under represention of right hemispheric strokes (67 = 33% in group S vs. 716 = 46% in O), due to the inherent definition of this scale.

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ORIGINAL ARTICLE

Severe stroke: patient profile and predictors of favorable outcome

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Summary. *Background:* Severe stroke carries high rates of mortality and morbidity. The aims of this study were to determine the characteristics of patients who initially presented with severe ischemic stroke, and to identify acute and subacute predictors of favorable clinical outcome in these patients. *Methods:* An observational cohort study, Acute Stroke Registry and Analysis of Lausanne (ASTRAL), was analyzed, and all patients presenting with severe stroke – defined as a National Institute of Health Stroke Scale score of ≥ 20 on admission – were compared with all other patients. In a multivariate analysis, associations with demographic, clinical, pathophysiologic, metabolic and neuroimaging factors were determined. Furthermore, we analyzed predictors of favorable outcome (modified Rankin scale score of ≤ 3 at 3 months) in the subgroup of severe stroke patients. *Results:* Of 1915 consecutive patients, 243 (12.7%) presented with severe stroke. This was significantly associated with cardio-embolic stroke mechanism (odds ratio [OR] 1.74, 95% confidence interval [CI] 1.19–2.54), unknown stroke onset (OR 2.35, 95% CI 1.14–4.83), more neuroimaging signs of early ischemia (mostly computed tomography; OR 2.65, 95% CI 1.79–3.92), arterial occlusions on acute imaging (OR 27.01, 95% CI 11.5–62.9), fewer chronic radiologic infarcts (OR 0.43, 95% CI 0.26–0.72), lower hemoglobin concentration (OR 0.97, 95% CI 0.96–0.99), and higher white cell count (OR 1.05, 95% CI 1.00–1.11). In the 68 (28%) patients with favorable outcomes despite presenting with severe stroke, this was predicted by lower age (OR 0.94, 95% CI 0.92–0.97), preceding cerebrovascular events (OR 3.00, 95% CI 1.01–8.97), hypolipemic pretreatment (OR 3.82, 95% CI 1.34–10.90), lower acute temperature (OR 0.43, 95% CI 0.23–0.78), lower subacute glucose concentration (OR 0.74, 95% CI 0.56–0.97), and spontaneous or treatment-induced recanalization (OR 4.51, 95% CI 1.96–10.41). *Conclusions:* Severe stroke presentation is predicted by multiple clinical, radiologic and metabolic variables, several of which are modifiable. Predictors in the 28% of patients with favorable outcome despite presenting with severe stroke include hypolipemic pretreatment, lower acute temperature, lower glucose levels at 24 h, and arterial recanalization.

Keywords: cerebrovascular disease, computed tomography, outcome, severe, stroke, thrombolysis.

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Introduction

Acute ischemic strokes with an initially severe neurologic deficit represent 2–10% [1] of all ischemic strokes, and are associated with poor short-term and long-term prognoses. They are usually termed 'malignant' or 'massive' if the total territory of the middle cerebral artery is infarcted [2]. Such patients have a high risk of focal edema with herniation, systemic complications such as pneumonia [3], acute cardiac failure [4], and death. These strokes seem to be more frequently caused by cardiac emboli and less frequently caused by large artery occlusive mechanisms than are less severe strokes [5]. In addition, increasing age, hyperglycemia and fever are often associated with worse outcomes. Although less evidence exists, several other factors may also predict a worse prognosis after stroke: premorbid disability, cognitive impairment, reduced consciousness at onset, certain acute clinical deficits, non-stroke unit care, and female gender [6]. The most consistently found predictors of long-term disability after ischemic stroke are increasing age and severity at onset [7]. Neuroimaging may represent a promising means to identify patients with poor outcome. The extent of early ischemic change on non-contrast computed tomography (CT) is associated with irreversible ischemia and prognosis [8–15]. In this study, we studied a population with clinically severe strokes.

Few studies have systematically evaluated multimodal factors in unselected consecutive severe stroke patients. A better knowledge of the risk factors in the acute and the subacute phases and the relationship between patient characteristics and long-term outcome would be useful for patient management. The objectives of this study were as follows: first,

to study the sociodemographic, clinical, biological and radiologic factors that are associated with severe stroke in the acute phase; and second, to define predictors of good recovery in patients who presented with severe stroke.

Methods

Patients

We used data from the Acute Stroke Registry and Analysis of Lausanne (ASTRAL). The ethics commission for research on humans of the Canton of Vaud, subcommission III, approved the scientific use of ASTRAL, which collected multiple datasets on all acute ischemic stroke patients from the period 2004 to 2010, defined arbitrarily as those presenting within 24 h after last-well time to the stroke unit and/or intensive care unit of Centre Hospitalier Universitaire Vaudois (CHUV) [16], which is a community hospital for a population of ~ 350 000, as well as the only stroke unit for 720 000 persons. In summary, we collected data on demographics, vascular risk factors, previous cerebrovascular events, prestroke disability, and medication at the time of stroke. Stroke pathophysiology was classified according to the TOAST classification [17]. The National Institute of Health Stroke Scale (NIHSS) score was prospectively recorded for each patient on admission, and at 4–6 h, 24 h, and 7 days, by NIHSS-certified medical personnel. Given the widespread use of the NIHSS to evaluate stroke severity, we used this scale with an arbitrary cut-off of ≥ 20 on admission to define severe strokes. As is the case for mild stroke, there is no consensus on how to define severe strokes. In this study, we propose this term for clinically severe strokes, and we used a cut-off of an NIHSS score of ≥ 20 points at presentation, while being aware of the limitations of the NIHSS grading of strokes associated with different cerebrovascular locations [16]. Metabolic and hematologic parameters and vital signs were recorded in the registry on arrival, and again at 24–48 h after stroke onset. Finally, we recorded silent lesions, leukoaraiosis and early ischemic lesions on acute imaging (mostly CT), as well as > 50% arterial stenosis or occlusion in cervical and cerebral arteries on acute imaging (mostly CT angiography). Most patients also underwent repeat parenchymal (magnetic resonance imaging or CT) and arterial imaging (by magnetic resonance angiography [MRA], computerized tomography angiography [CTA], or Doppler) in the subacute or chronic phase after stroke. The modified Rankin score (mRs) was assessed by mRs-certified personnel at 3 months in the outpatient clinic. At 12 months, and for patients unable to attend the 3-month outpatient clinic, mRs was assessed by a structured telephone interview by mRs-certified personnel. Acute stroke management and secondary prevention of these patient followed current European Stroke Organization guidelines [18].

Statistical analyses

In the first part of this study, all ASTRAL patients were separated into a group with a severe stroke (S) with an admission NIHSS score of ≥ 20, or other comparison group (O). We analyzed all demographic, clinical, biological and radiologic factors (total of 67 variables) that were readily available in the acute phase of stroke and were collected in ASTRAL.

For the second part of this study, all patients in the S group were separated into a group with a relatively favorable outcome and a group with an unfavorable outcome. Favorable outcome was defined as an mRS score of ≤ 3, which is a common cut-off value in studies of severe stroke, such as hemorrhagic or posterior fossa stroke studies, and, given the initially severe clinical picture, made it a priori less probable that an mRS score of 0, 1 or 2 would be achieved. We first studied the factors from the acute phase that may be associated in severe stroke with a favorable outcome, and then added variables collected in the subacute phase (24–48 h after stroke), including subacute NIHSS values, metabolic values, recanalization on repeat arterial imaging, and parenchymal findings in subacute neuroimaging.

For univariate comparison, we used Student's *t*-test for normally distributed continuous data, and the Wilcoxon test for skewed distributions. For the categorical data, we used the chi-squared test. All variables with *P*-values of < 0.1 in the univariate analysis were entered into a multivariate logistic regression model to identify independent predictors. Using the significant variables in the multivariate analysis, we calculated the areas under the receiver operating characteristic curves (ROC-AUCs) for the two analyses. The level of significance was set at 95%. All data analyses were conducted by a statistician of the Institute of Social & Preventive Medicine at the CHUV, with STATA version 9.2, 2001 (Stata, College Station, TX, USA).

Results

Two hundred and forty-three of 1915 (12.7%) consecutive stroke patients had presented with severe stroke. Regarding the 58 factors examined from the acute phase, there were important baseline differences between the S and O groups (selected variables are shown in Table 1). Patients in the S group were more likely to be female (53.50%), to have atrial fibrillation, and to have a low ejection fraction. Higher percentages of dissection and cardiac etiology were found in these patients, none of whom had lacunar stroke. Also, the proportion of patients with unknown day of onset of symptoms was higher in the the S group than in the O group, as was the proportion of patients with prestroke disability and pre-existing neurologic deficit. Hypertension and chronic ischemic lesions were less frequent in the S group, but occlusion or stenosis of the cervical and/or cerebral vessels in the ischemic territory was more frequent in the S group. Patients in the S group had higher heart rates and leukocytosis at admission, but lower body temperature, hemoglobin levels, and hematocrit.

Multivariate analysis yielded seven stroke-related, metabolic and radiologic variables that were independently associated with severe stroke (Table 2). The ROC-AUC for predicting

Table 1 Selected patient characteristics in the acute phase in the 'severe' and 'others' groups with univariate comparisons

Patient characteristics	All (n = 1915)	Severe (n = 243)	Others (n = 1672)	OR	P-value
Demographics					
Age (years), mean (± SD)	68.8 (15.4)	69.6 (16.8)	68.7 (15.2)	1.00	0.37
Female sex	840 (43.9)	130 (53.5)	710 (42.5)	0.64	< 0.01
Prestroke disability (measured with mRS)	0 (1)	0 (1)	0 (1)	1.17	0.01
NIHSS and its course					
Prestroke neurologic deficit (measured with NIHSS)	0 (0)	0 (0)	0 (0)	1.13	0.03
Admission NIHSS score	6 (11)	23 (5)	5 (7)	–	–
NIHSS score at 4–6 h after arrival	5 (9)	23 (6)	4 (7)	1.55	< 0.01
NIHSS score at 24 h	4 (9)	22 (8)	3 (6)	1.31	< 0.01
NIHSS score at 7 days	3 (8)	22 (21)	2 (4)	1.15	< 0.01
Risk factors (pre-existing or newly discovered)					
Hypertension	1280 (66.9)	140 (57.8)	1140 (68.2)	0.63	< 0.01
Diabetes mellitus	303 (15.9)	33 (13.7)	270 (16.2)	0.82	0.33
Active smoking	444 (23.5)	46 (19.8)	398 (24.0)	0.78	0.16
Atrial fibrillation	482 (25.2)	94 (38.8)	388 (23.2)	2.09	< 0.01
Coronary heart disease	284 (14.8)	37 (15.2)	247 (14.7)	1.03	0.86
Low ejection fraction (< 35%)	85 (4.5)	20 (8.6)	65 (3.9)	2.27	0.02
Previous cerebrovascular event (stroke, TIA, or retinal)	28 (1.4)	3 (1.2)	25 (1.5)	0.77	0.11
Medication at admission					
Antiplatelet	681 (35.9)	81 (33.8)	600 (36.2)	0.90	0.48
Anticoagulant	192 (10.1)	29 (12.1)	163 (9.8)	1.26	0.28
Antihypertensive	1045 (55.2)	123 (51.9)	922 (55.7)	0.85	0.27
Hypolipemic	438 (23.1)	41 (17.2)	397 (24.0)	0.65	0.02
Antidiabetic	155 (8.1)	14 (5.8)	141 (8.5)	0.66	0.16
Stroke onset during night sleep	445 (23.2)	49 (20.1)	396 (23.7)	0.81	0.22
Unknown stroke onset, not sleep	97 (5.0)	32 (13.1)	65 (3.8)	3.74	< 0.01
Stroke mechanism					
Atherosclerosis	254 (13.6)	30 (12.5)	224 (13.7)	0.90	0.61
Unknown	458 (24.5)	50 (20.9)	408 (25.0)	0.91	0.72
Cardiac (including patent foramen ovale as the likely cause)	617 (33.0)	118 (49.3)	499 (30.6)	1.76	0.01
Lacunar	277 (14.8)	0 (0)	277 (17.0)	–	–
Dissection	92 (4.9)	18 (7.5)	74 (4.7)	1.81	0.07
Other and rare causes	77 (4.1)	11 (4.6)	66 (4.0)	1.24	0.56
Multiple and coexisting causes	92 (4.9)	12 (5.0)	80 (4.9)	1.02	0.76
Radiologic findings					
Acute parenchymal findings	632 (35.5)	149 (63.4)	483 (31.2)	3.80	< 0.01
Chronic radiologic strokes	514 (30.8)	55 (24.5)	459 (31.7)	0.69	0.03
Significant arterial findings in ischemic territory	796 (49.9)	616 (88.2)	180 (44.2)	9.43	< 0.01
Metabolic values at admission					
Admission systolic blood pressure (mmHg), mean (± SD)	158.87 (28.5)	156.44 (31.4)	159.22 (28.0)	0.99	0.16
Admission heart rate (min^{-1}), mean (± SD)	79.97 (18.0)	83.78 (22.3)	79.41 (17.2)	1.01	< 0.01
Admission temperature (°C), mean (± SD)	36.39 (0.6)	36.26 (0.8)	36.41 (0.6)	0.70	< 0.01
Admission glucose (mM), mean (± SD)	7.17 (2.9)	7.55 (2.3)	7.11 (3.0)	1.03	0.05
Admission hemoglobin ($g\ L^{-1}$), mean (± SD)	138.77 (32.8)	132.86 (19.6)	139.65 (34.3)	0.98	< 0.01
Admission white cell count ($10^3\ L^{-1}$), mean (± SD)	8.65 (4.4)	9.83 (4.7)	8.48 (4.3)	1.06	< 0.01
Interventions and outcome					
Intravenous thrombolysis	302 (15.7)	72 (29.6)	230 (13.7)	2.72	< 0.01
Endovascular treatment	16 (0.8)	7 (2.8)	9 (0.5)	6.77	< 0.01
Craniectomy	15 (0.7)	9 (3.7)	6 (0.3)	10.66	< 0.01
mRS score at 3 months	2 (3)	5 (3)	1 (2)	1.93	< 0.01
Favorable outcome (mRS score at 3 months of 0–3)	1405 (73)	68 (2)	1337 (7)	0.10	< 0.01

mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; SD, standard deviation; TIA, transient ischemic attack. Values are expressed as median and interquartile range for continuous variables, or absolute count and percentage for categorical variables, unless stated otherwise.

severe strokes was 86% with the significant variables from the acute phase.

Sixty-eight of 243 (28.0%) of consecutive severe stroke patients had a favorable outcome at 3 months. Selections of the 63 acute and 31 subacute variables examined are shown in Tables 3 and 4, respectively. In a multivariate analysis of the acute phase (Table 5), favorable outcome was predicted by lower age and lower initial temperature. Private insurance status, lower pre-existing functional handicap, lower glycemia and recanalization treatment also increased the probability of favorable outcome. When subacute variables were added into the multivariate analysis (Table 6), treatment with hypolipemic

Table 2 Multivariate analysis of factors significantly associated with S

Factors	OR (95% CI)	*P*-value
Cardioembolic stroke	1.74 (1.19–2.54)	< 0.01
Unknown onset of stroke (but not wake-up strokes)	2.35 (1.14–4.83)	0.02
Early ischemic changes on initial imaging	2.65 (1.79–3.92)	< 0.01
Chronic strokes on imaging	0.43 (0.25–0.71)	< 0.01
Significant arterial findings in ischemic territory	27.01 (11.59–62.92)	< 0.01
Hemoglobin (g L^{-1})	0.97 (0.96–0.98)	< 0.01
White cell count (× 10^3 L^{-1})	1.05 (1.00–1.10)	0.04

CI, confidence interval; OR, odds ratio.

agents (mostly statins) increased the probability of favorable outcome. The pre-existing functional handicap was replaced by past cerebrovascular events, acute by subacute (24–48 h) glycemia, and recanalization treatment by (therapeutic or spontaneous) recanalization. The ROC-AUCs for predicting favorable outcome after severe stroke with the acute variables were 82% and 81% when the subacute variables were added.

Discussion

Using a large number of sociodemographic, clinical, radiologic and metabolic variables, we have identified seven factors that are associated with severe stroke at the time of emergency room admission. Furthermore, we found that favorable outcome despite the patient initially presenting with severe stroke was associated, with a high degree of confidence, with demographic and metabolic factors and early recanalization.

When examining the profile of patients who suffer severe stroke, we found cardio-embolic origin of stroke to be significantly associated with these patients, similarly to previous studies [19–21]. This may be explained by the usual size of cardiac emboli as well as by the lack of collateral vascularization, which may develop and compensate for acute arterial occlusion in patients with gradual occlusion of arteries, such as in atherosclerosis of cervical or cerebral arteries. In the univariate, but not the multivariate, analysis, we also found dissection to be associated with severe stroke. It is of note that there were no patients with lacunar stroke among those presenting with severe stroke.

We found that severe strokes were more frequently of unknown time of onset, but only if they were not associated with sleep onset. This is possibly related to the fact that such patients were not alert and were unable to express details of their stroke onset. The reason why this is not the case for sleep-onset stroke may be that such strokes are more frequently lacunar [22]. Severe strokes were more frequent in patients with lower hemoglobin levels, suggesting that decreased oxygen transport capacity may increase infarct size, consistent with a previous report [23]. White cell count has previously been associated with a more severe clinical presentation and with a worse early stroke outcome [24]. It is not clear whether this is a direct effect of white cell activity and inflammation in the lesioned brain, or whether it is rather a marker of associated conditions (e.g. fever, early infection, or stress response) that may increase stroke severity and worsen outcome.

Table 3 Selected patient characteristics in the acute phase in the favorable outcome and unfavorable outcome groups, with univariate comparisons

Patient characteristics	All patients (n = 243)	Favorable outcome (mRS score of 0–3 at 3 months: n = 68)	Unfavorable outcome (mRS score of 4–6 at 3 months: n = 175)	OR	*P*-value
Age (years), median (± IQR)	69.6 (16.88)	72.8 (16.1)	61.4 (16.2)	0.96	< 0.01
Private insurance	42 (17.4)	17 (25.0)	25 (14.4)	1.97	0.06
mRS score prestroke, median (± IQR)	0 (1)	0 (0.5)	1 (2)	1.17	0.01
Hypolipemic treatment on admission	41 (17.2)	15 (22.7)	26 (15.1)	1.65	0.17
Unknown stroke onset (not sleep)	32 (13.1)	7 (10.2)	25 (14.2)	0.68	0.41
Acute parenchymal findings	149 (63.4)	37 (56.9)	112 (65.8)	0.68	0.20
Chronic radiologic strokes	55 (24.5)	13 (21.6)	42 (825.6)	0.80	0.54
Significant arterial findings in ischemic territory	180 (88.2)	56 (90.3)	124 (87.3)	1.35	0.54
Systolic blood pressure (mmHg)	156.44 (31.4)	149.41 (28.7)	159.19 (32.0)	0.98	0.03
Temperature (°C)	36.26 (0.8)	36.07 (0.6)	36.33 (0.8)	0.63	0.02
Glucose (mM)	7.55 (2.3)	6.85 (1.8)	7.82 (2.5)	0.81	0.01
White blood cell count (× 10^3 L^{-1})	9.83 (4.7)	9.93 (4.7)	9.79 (4.7)	1.00	0.84
Total cholesterol (mM)	5.59 (4.4)	5.08 (1.5)	5.77 (5.0)	0.94	0.37
IVT	72 (29.6)	32 (47.0)	40 (22.8)	3.30	< 0.01
EVT	7 (2.8)	3 (5.8)	3 (1.7)	5.50	0.03
IVT or EVT	79 (32.5)	36 (52.9)	43 (24.5)	3.45	< 0.01
Timing of intervention (min)	152.1 (91.6)	13.41 (4.9)	13.00 (5.4)	1.00	0.39
Craniectomy	9 (3.7)	3 (4.4)	6 (3.4)	1.30	0.72

EVT, endovascular treatment; IQR, interquartile range; IVT, intravenous thrombolysis; mRS, modified Rankin scale; OR, odds ratio. Values are expressed as mean and standard deviation for continuous variables, or absolute count and percentage for categorical variables, unless stated otherwise.

Table 4 Selected factors of the acute phase in the favorable outcome and unfavorable outcome groups, with univariate comparisons

Patient characteristics	All patients	Favorable outcome (mRS score of 0–3 at 3 months)	Unfavorable outcome (mRS score of 4–6 at 3 months)	OR	*P*-value
N (%)	243 (100)	69 (28)	174 (72)	–	–
Subacute imaging findings at 24–48 h					
Any stroke-related findings (ischemia and/or hemorrhage)*	150 (96.1)	51 (92.7)	99 (98.0)	0.25	0.13
Any hemorrhagic transformation (symptomatic or not)	29 (18.9)	10 (18.5)	19 (19.1)	0.95	0.919
Symptomatic hemorrhagic transformation according to ECASS-2 definition	6 (3.9)	0 (0.0)	6 (6.0)	–	–
Subacute vascular imaging at 24–48 h					
Significant arterial findings in ischemic territory	78 (67.2)	27 (60.0)	51 (71.8)	0.58	0.19
Partial or complete recanalization of cervical and/or cerebral arteries (where assessed)	66 (28.3)	35 (51.4)	31 (18.7)	4.58	< 0.01
Excracranial recanalization (complete, partial)	20 (8.5)	6 (8.8)	14 (8.4)	1.05	0.92
Intracranial recanalization (complete, partial)	63 (27.1)	37 (54.4)	26 (15.8)	6.33	< 0.01
Subacute metabolic values at 24–48 h					
Systolic blood pressure (mmHg)	143.47 (21.9)	139.78 (21.9)	145.07 (21.8)	0.98	0.1
Diastolic blood pressure (mmHg)	68.70 (15.6)	67.55 (15.7)	69.19 (15.5)	0.99	0.472
Heart rate (min^{-1})	82.55 (18.3)	76.25 (16.6)	85.26 (18.3)	0.97	< 0.01
Temperature (°C)	37.01 (0.7)	36.89 (0.7)	37.06 (0.6)	0.69	< 0.01
Glucose (mM)	6.41 (1.9)	5.93 (1.2)	6.65 (2.1)	0.77	0.02
Serum creatinine (mM)	89.53 (71.7)	79.19 (25.4)	93.48 (82.6)	0.99	0.16
Hemoglobin (g L^{-1})	126.59 (19.5)	124.48 (20.7)	127.53 (19.0)	0.99	0.4
Hematocrit mean (± SD)	38.04 (5.3)	37.19 (5.3)	38.41 (5.3)	0.95	0.22
Total cholesterol (mM)	8.12 (9.3)	4.84 (1.0)	9.76 (11.2)	0.90	0.35
White blood cell count (× 10^3 L^{-1})	11.21 (3.9)	10.69 (3.3)	11.45 (4.1)	0.94	0.29
Platelet count (× 10^3 L^{-1}) (mean)	215.95 (74.3)	218.71 (67.4)	214.71 (77.5)	1.00	0.77
NIHSS score at 7 days, median (± IQR)	22 (21)	12 (15)	24 (24)	0.85	< 0.01
Discharge*					
Death	84 (36.5)	0 (0)	84 (50.9)	–	–
Home	11 (4.7)	9 (13.8)	2 (1.2)	13	< 0.01
Long-term institution	14 (6.0)	0 (0)	14 (8.4)	–	–
Transfer to other acute-care service or hospital	41 (17.8)	19 (29.2)	22 (13.3)	2.68	< 0.01
Rehabilitation hospital	80 (34.7)	37 (56.9)	43 (26.0)	3.74	< 0.01

IQR, interquartile range; mRS, modified Rankin scale; OR, odds ratio; SD, standard deviation. Values are expressed as mean and SD for continuous variables, or absolute count and percentage for categorical variables, unless stated otherwise. *Not included in the multivariate analysis.

Radiologic data revealed that early signs of parenchymal ischemia and notable clinical findings within arteries of the ischemic region (e.g. occlusion or > 50% stenosis) are observed significantly more frequently in patients with severe stroke, again confirming the findings of previous studies [25,26].

We also found that chronic strokes on neuroimaging are less frequent among severe stroke patients. This seems counterintuitive, given that functional compensation for cerebral damage depends partially on the remaining 'healthy' brain. However, patients who have less severe strokes might have a higher likelihood of having survived other minor strokes in the past. In addition, such survivors of previous strokes may receive better secondary prevention treatments, which have been shown to decrease not only recurrence, but also the severity of recurrent strokes [27–30].

Although female gender and increased heart rate were more frequent in those patients presenting with severe stroke by univariate analysis, these factors were not independent. Similarly, pre-existing hypertension and pretreatment with hypolipemic agents were negatively associated with severe stroke in the univariate, but not in the multivariate, analysis. Interest-

Table 5 Multivariate analysis of acute-phase factors significantly associated with favorable ourtcome

Factors	OR (95% CI)	*P*-value
Age	0.95 (0.92–0.97)	< 0.01
Prestroke handicap (mRS)	0.62 (0.40–0.95)	0.03
Private insurance status	2.51 (1.05–5.98)	0.037
Acute temperature	0.42 (0.23–0.74)	< 0.01
Acute glucose value	0.74 (0.61–0.90)	< 0.01
Acute EVT within recommended time limits (IVT or EVT)	2.47 (1.20–5.08)	0.01

CI, confidence interval; EVT, endovascular treatment; IVT, intravenous thrombolysis; mRS, modified Rankin scale; OR, odds ratio.

Table 6 Multivariate analysis of factors of the acute and subacute phases combined that are significantly associated with favorable outcomeF

Factor	OR (95% CI)	*P*-value
Age	0.94 (0.91–0.97)	< 0.01
Previous cerebrovascular event (stroke, TIA, retinal ischemia)	3.00 (1.00–8.96)	0.04
Hypolipemic treatement at stroke onset	3.82 (1.34–10.89)	0.01
Acute temperature	0.42 (0.23–0.78)	< 0.01
Subacute glucose values at 24–48 h	0.73 (0.56–0.96)	0.02
Recanalization of cervical and/or intracranial arteries (partial or complete)	4.51 (1.95–10.40)	< 0.01

CI, confidence interval; OR, odds ratio; TIA, transient ischemic attack.

ingly, age, pre-existing risk factors, such as hypertension, diabetes, or smoking, and insurance status were not associated with severe stroke.

As an additional observation, the in-hospital course of NIHSS score differed between the two groups: in the less severe strokes, NIHSS score measured at 4 h, 24 h and 7 days showed a decreasing pattern from the beginning, which was not the case for severe strokes, where the NIHSS score remained elevated for the first 7 days. This result is probably attributable to an increased rate of complications in severe stroke patients, such as brain edema, hemorrhagic transformation (HT), and medical complications [1,2,31,32]. Regarding HT according to the ECASS-2 definition, unfavorable outcome was associated with greater HT.

Given that stroke severity is one of the most significant independent predictors of poor short-term and long-term outcome [33–35], we were interested in analyzing predictors of favorable outcome after 3 months in patients with severe stroke.

As expected, higher age and prestroke handicap (as measured by previous mRS score) were associated with a reduced likelihood of achieving a favorable outcome at 3 months in severe stroke patients. A reduction in the number of synapses in old age [36] and a diminished volume of cortical gray matter [37] may hinder recovery, because of limited neuronal plasticity. Also, acute initial temperature and elevated glucose levels had a negative influence on outcome, as previously shown [38,39]. The relationship between temperature, inflammation, stroke severity and stroke outcome is currently being elucidated [40]. However, stroke severity may be more frequently associated with dysphagia during the acute phase, which may lead to aspiration pneumonia and further worsening of stroke outcome [41].

Private insurance status – probably indicating a higher socioeconomic status – has previously been show to predict favorable outcome in stroke patients [42,43]. The reasons for this observation are not certain, although one of our previous studies showed lower initial stroke severity in privately insured patients [42]; this was not confirmed in the current dichotomized study.

It is encouraging that recanalization also favorably influenced the fate of severe stroke patients. It has been hypothesized that the decreased effect of intravenous thrombolysis in severe stroke may be related to insufficient recanalization [44,45]. Most patients with severe stroke have large occluding thrombi in intracranial arteries, which may need endovascular treatment for effective recanalization [46]; although only few of our patients underwent such treatments, an effective recanalization strategy should be offered to severe stroke patients, particularly if the relationship between viable brain tissue and core is favorable [47].

When we added covariates from the subacute phase, we found that previous clinical cerebrovascular events (stroke, transient ischemic attack, and retinal ischemia) were independently associated with favorable outcome at 3 months. This was not explained by the stroke mechanism, but could indicate that patients who recovered from a previous stroke (rather than died) also had a better chance of recovery from a subsequent severe stroke; this could be partly explained by the genetics of neurovascular factors, the anatomy of the cervico-cerebral vasculature, including collaterals, or ischemic preconditioning [48].

As recently shown for ischemic stroke of any severity, pretreatment with hypolipemic agents (mostly statins in our population) was also associated with favorable outcome [49]. This may be explained by the pleiotropic effects of statins, especially on the cerebral vasculature. Finally, hyperglycemia in the subacute phase seemed to be associated with unfavorable outcome at least as strongly as in the acute phase. This confirms previous observations of our group [50].

Interestingly, pre-existing risk factors and stroke etiology were not associated with 3-month outcome.

One limitation of our work is its observational, single-center design. Furthermore, we did not include a detailed analysis of perfusion imaging studies or of collaterals in our analysis, even though such factors have been shown to be linked to outcome prediction in stroke patients [51,52]. The fact that only a few patients had endovascular treatment limited the ability to explore its effects; recanalization (spontaneous or thrombolysis-related) was frequently measured, however, and showed

significant associations with favorable outcome. We also accept that the criterion of an NIHSS score of ≥ 20 leads to a slight underrepresention of right hemispheric strokes (67 = 33% in the S group vs. 716 = 46% in the O group), owing to the inherent definition of this scale.

In summary, our results show that prestroke characteristics of the patient, stroke etiology, hematologic values and acute radiologic and arterial findings are associated with severe stroke. Although some of the results were expected, others are new, and most can be influenced before or after onset of the severe stroke. As expected, severe stroke patients had a rather poor prognosis. Nevertheless, several factors associated with favorable outcome, such as lower acute temperature, lower glucose levels at 24 h, previous cerebrovascular events, and arterial recanalization, should encourage clinicians to treat such patients aggressively and to search for new treatment modalities.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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