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Early predictors of 30-day mortality in supratentorial ischemic stroke patients – first episode

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SUMMARY

Introduction: Prognostic factors following stroke remain to be established. The aim of this study was to determine early prognostic factors related with a 30-day mortality in first episode ischemic stroke patients.
Materials and methods: The study group comprised 329 consecutive patients, aged between 33 and 99 years (mean age±SD 69±12.6) admitted within 24 hours following their first supratentorial ischemic stroke, confirmed either by computer tomography (CT) and/or autopsy. The following data were assessed within 24 hours of hospitalization: gender, age, history of diabetes mellitus, history of ischemic heart disease, obesity, the neurological deficit at entry and after one day, level of consciousness at entry and after one day, electrocardiographic dysrhythmia at entry, blood pressure at entry and body temperature on the first day following stroke. We also assessed particular serum biochemical and hematological markers including: hematocrit, fibrinogen concentration, platelet count, white blood cell (WBC) count, gamma globulin level, glucose level, cholesterol level, the erythrocyte sedimentation rate (ESR), and creatinine kinase (CK) level. The end-point for assessment was early death (within 30 days). Statistical analysis consisted of univariate analysis and multiple regression.
Results: Univariate analysis demonstrated that an older age, increased neurological deficit at entry and on the next day, decreased consciousness at entry and on the next day, electrocardiographic dysrhythmia, increased body temperature and glucose level, decreased cholesterol level and increased CK level were significantly associated with death after 30 days ($p \leq 0.05$). During multivariate analysis, only a severe neurological deficit (Scandinavian Stroke Scale ≤15 points) both at entry and on the next day (OR=8.3; 95% CI: 2.83–24.35), decreased consciousness within the first 24 hours of hospitalization (OR=19.2; 95% CI: 2.84–127.77) and electrocardiographic dysrhythmia (OR=5.2; 95% CI: 2.37–13.77) were associated with death after 30 days.
Conclusion: A severe neurological deficit lasting 24 hours, decreased consciousness within 24 hours of hospitalization and electrocardiographic dysrhythmia are the most important indicators of 30-day mortality in patients with first-time ischemic stroke.

INTRODUCTION

Despite the decreased mortality rate observed in the past two decades, stroke remains the major cause of death and residual disability in highly developed countries [1]. During the past few years, great efforts have been made to determine factors influencing the adverse outcome during the acute phase of stroke. Early recognition of possible predictors seems essential for optimizing therapeutical procedures, especially those, which are cost- and time-consuming. This is extremely important in countries such as Poland, where financial and technical resources are limited. New treatment methods such as thrombolytic therapy, require clearly defined indications that need to be deter-

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mined within the first few hours following stroke due to a narrow therapeutical window [2].

Factors that predict an adverse outcome or an increased mortality include: increased age [3–7], severe neurological deficit on admission [3,8–11], decreased consciousness on admission [12–14], presence of diabetes mellitus [15–18], atrial fibrillation [19–21], fever [22,23] and incontinence [21,24]. Other studies have demonstrated the possible predictive role of impaired proprioception [25], hemianopia [6,26] and a history of congestive heart failure [13]. We also evaluated the significance of normal (routine) laboratory tests as predictors of a negative outcome or increased mortality. These results suggest that an elevated ESR [4,27], increased hematocrit, leukocytosis [27], hyperglycemia [4,28] and ECG or EEG abnormalities [14], can be considered as potential prognostic factors.

Other predictive factors include a correlation between the neuron-specific enolase/carnosinase ratio and a worse 90-day outcome [29]. Another group [30] suggested S-100 protein and neuron-specific enolase serum levels as predictors of a worse outcome, while yet another demonstrated a correlation between the abnormally low protein C level and increased mortality after six months [31]. One study suggested an association between poor stroke outcome and lower cholesterol concentration [32].

Several studies that examined early CT findings during acute stroke concluded that the presence of a hyperdense middle cerebral artery sign [33–36] and infarct size [14,37] are both correlated with a negative outcome. One group demonstrated an elevated positive predictive value of infarct volume measured by means of the SPECT technique, which predicted daily living activity impairment one year following cerebral ischemia [38]. Finally another group described the predictive role of the ultrasound examination in patients with carotid stroke [39].

There has been no general consensus as to whether a battery of scales and dependent variables, or rather just one simple test, should be used in predicting the outcome of stroke (acute phase).

Previous study results are inconsistent, mainly because of observation period differences, varying definitions of the term 'outcome' and different dependent variables. Additionally, some studies concerned different sets of demographic data and different clinical signs and symptoms.

Stroke mortality in Poland, considered to be a Central European country, is still very high in comparison to Western European countries [40] (the 28-day mortality rate) [41]. Thus, we decided to investigate the predictors of early mortality in first episode ischemic stroke patients.

MATERIALS AND METHODS

Our study group comprised 329 ischemic stroke patients, admitted to the Stroke Unit, Department of Neurology, within 48 hours following stroke. Cerebral ischemia was determined clinically and confirmed by computer tomography (CT) and/or autopsy. A medical history was collected in order to establish whether there had been a previous stroke, were there any stroke risk factors including hypertension, diabetes mellitus, ischemic heart disease, or congestive heart failure. These risk factors were grouped into classes: patients with diabetes mellitus scored 1, and without- scored 0. We estimated the stroke severity according to the Scandinavian Stroke Scale (SSS) [20], both on the day of admission (Day 0) and on Day 1. Patients that scored ≤15 points on the SSS were considered to have a 'severe deficit' while those with >15 points were considered to have a 'slight deficit'.

The level of consciousness both on admission and the following day were graded on a subscale of the SSS, which comprised 'coma, stupor, somnolence, and normal alertness'. During uni- and multi-variate analyses patients with normal alertness were graded as '0', and patients with consciousness disturbances were graded as '1'. On admission we performed blood pressure measurements and an ECG. We determined whether the patient presented with atrial fibrillation or other cardiac dysrhythmia.

The following routine biochemical and hematological parameters were collected after 12 hours of fasting: hematocrit, WBC count, platelet count, fibrinogen concentration, gamma globulin level, glucose level, total cholesterol level, ESR and CK activity. When identifying independent predictors of a negative outcome, baseline biochemical and hematological values, were graded as '0' (laboratory normal values) and '1' (above normal laboratory values). Table 1 presents normal laboratory values.

We evaluated the hematocrit, WBC and platelet counts by means of the photometric method (Vega, Roche), the fibrinogen concentration by means of the coagulometric method (Beringher), the gamma globulin level and CK activity by means of the enzymatic method (Hitachi), and the ESR by means of

Table 1. Normal laboratory hematological and biochemical parameter values assessed in the study.

Parameter	Normal range	Unit
Hematocrit	33 - 44 (women) 38 - 49 (men)	%
Fibrinogen	1.8 - 3.5	g / L
Platelet count	130000 - 350000	1/mm^3
White blood cell count	4000 - 10000	1/mm^3
Gamma globulin level	8 - 17	g / L
Cholesterol level	< 5.2	mmol / l
Erythrocyte sedimentation rate	< 5	mm / h
Creatinine kinase activity	< 190	U / L

the Westergren method. The serum glucose level was measured by means of the photometric method and total cholesterol was assayed by means of the enzymatic method (CHOD-PAP), using commercially available kits (RA-1000, Boeringer-Mannheim).

Patients were followed up for 30 days following stroke. We recorded mortalities and differentiated the cause of death, according to the Oxfordshire Scale [42].

Statistical analysis

Univariate analysis with the chi-squared test and the Student's t-test were used when needed. The SSS score was reported as a median value (25th–75th percentiles). The Mann-Whitney U test was used for neurological deficit comparison in SSS score patients who died and those who survived. Significant variables during univariate analysis were subject to multivariate regression in order to identify data independently affecting the 30-day mortality.

RESULTS

Table 2 demonstrated the overall comparison of demographic data, vascular risk factors and baseline clinical data of patients who survived and died within 30 days following stroke onset.

The overall patient age (329 patients) amounted to 70.0±12.6 years. Time of admission following stroke onset is presented in table 3.

The median SSS score value on Day 0 in deceased patients amounted to 7 (2–21) and those that survived 34 (24–41) ($p \leq 0.05$). On Day 1 they scored 5 (0–16) vs. 34 (24–42) ($p \leq 0.05$).

Out of 56 (17.2%) patients who died within 30 days following stroke, nine (16.1%) died due to brain edema, 31 (55.4%) due to cardiac complications and 16 (28.7%) due to other medical complications.

Table 2. Demographic data, vascular risk factors and baseline clinical data of patients who survived or died within 30 days following stroke onset.

Parameter	patients			
	Survivors		Deceased	
	n	%	n	%
Patients	273	82.8	56	17.2
Men	142	52	27	48.2
Women	131	48	29	51.8
Age (years) [mean±SD]	69.2±12.7*		74.3±11.3*	
Diabetes mellitus	74	27.1	15	26.8
Ischemic heart disease	148	54.2**	41	73.2**
Obesity	80	29.3	15	26.8
Hypertension	198	72.5	37	66.1
Severe neurological deficit on Day 0	48	17.6***	37	66.1***
Severe neurological deficit on Day 1	42	15.4#	40	71.4#
Decreased consciousness on Day 0	67	24.8##	34	61.4##
Decreased consciousness on Day 1	48	17.6###	38	68###
ECG evidence of dysrhythmia	97	35.7¤	39	70.4¤
Incontinence	63	23.5¤¤	36	64.3¤¤
Blood pressure on admission (mean±SD)	140.1±24.1		143.2±27.6	
Maximal body temperature during the first 24 hours of hospitalization	37.4±0.6¤¤¤		38.0±0.8¤¤¤	

* $p \leq 0.05$ (Student's t-test); ** $\chi^2=6.86$, $p=0.0088$; *** $\chi^2=0.95$, $p=0.0001$; # $\chi^2=0.75$, $p=0.00001$; ## $\chi^2=28.58$, $p=0.0001$; ### $\chi^2=60.83$, $p=0.00001$; ¤ $\chi^2=22.30$, $p=0.0001$; ¤¤ $\chi^2=37.51$, $p=0.00001$; ¤¤¤ $p \leq 0.05$ (Student's t-test)

Table 3. Time of admission following stroke onset

Time	Patients	
	n	%
0 - 6 hours	186	56.5
6 -12 hours	70	21.3
12-24 hours	55	16.7
24 - 48 hours	18	5.5

Table 4. Different levels of decreased consciousness in study patients.

Level of decreased consciousness	Time	patients			
		Survivors		Deceased	
		n	%	n	%
Somnolence	Day 0	39	14.5	11	22
	Day 1	22	8.2	10	20
Stupor	Day 0	17	6.3	9	18
	Day 1	17	6.4	9	18
Coma	Day 0	11	4.1	14	25
	Day 1	9	3.4	15	30

Table 4 presents various levels of decreased consciousness observed on Day 0 and on Day 1.

Patients that died presented with a higher mean maximal body temperature on Day 1 and more patients who died demonstrated a maximal body tem-perature ≥37.5°C (OR=3.02; 95% CI=1.56–5.81).

Atrial fibrillation was noted in 38.9% of patients who died and in 20% of survivors. This was the most frequent type of dysrhythmia.

Table 5 presents hematological and biochemical data of survivors and deceased patients within 30 days following stroke.

Patients who died within 30 days following stroke onset presented with an increased glucose level (≥6.4 mmol/l) (OR=2.75; 95% CI=1.47–5.14), CK activity (>100 IU) (OR=2.65; 95% CI=1.37–5.11) and lower cholesterol level (<5.2 mmol/l) (OR=0.44; 95% CI=0.23–0.85).

Independent predictors of death within 30 days following stroke, were based on baseline clinical and biochemical data and identified by means of regression analysis. These predictors comprised a severe neurological deficit (Scandinavian Neurological Score ≤15 points), both on Day 0 and on Day 1 (OR=8.3; 95% CI: 2.83–24.35), decreased consciousness on Day 0 or Day 1 (OR=19.2; 95% CI: 2.84–127.77) and electrocardiographic dysrhythmia on Day 0 (OR=5.2; 95% CI: 2.37–13.77).

Table 5. Hematological and biochemical data in patients who survived or died within 30 days following stroke onset.

	Patients	
	Survivors n=273	Deceased n=56
Hematocrit (%)	42.4±5.0	42.8±7.1
Fibrinogen (g/l)	2.9±0.9	2.7±0.8
Platelet count	229193±75279	237525±70122
White blood cell count	9 434±5 250	10 534±4 322
Gamma globulin level (g/l)	21.4±5.5	22.4±6.7
Glucose level (mmol/l)	6.7±2.4	4.9±2.1
Cholesterol level (mmol/l)	5.5±1.3*	4.9±1.3*
Erythrocyte sedimentation rate on Day 0	23.7±21.5	22.5±22.7
Erythrocyte sedimentation rate on Day 1	46.2±33.5	42.3±31.6
Creatinine kinase activity (IU)	47 (28-105)**	89 (42-231)**

* p≤0.05 (Studentís t-test); ** p≤0.05 (Mann-Whitney U test)

DISCUSSION

Knowledge of early predictors can influence the assessment of the benefit/risk ratio in treating patients with a poor prognosis, by identifying those patients and encouraging physicians to apply a more aggressive method of treatment. Early diagnosis enables an appropriate selection of patients who can benefit from advanced methods of therapy. It seems especially important in countries such as Poland, where access to advanced diagnostic and therapeutical methods remains technically and financially limited. Knowledge of early predictors also allows for the qualification and stratification of patients to be included in drug trials.

Current retrospective study results are consistent with previous studies using multivariate analysis. This study demonstrated that basic clinical data such as a neurological deficit, decreased consciousness and dysrhythmia are the most useful predictors of mortality during the acute phase of stroke.

It seems almost impossible to establish the predictive value of many parameters. This is due to observation period differences, different study endpoints, clinical symptom rating scales, inclusion criteria and non-comparable methods of statistical analysis. Most previous results have been determined by means of univariate analysis. Some results are difficult to use during everyday practice.

They often include sophisticated biochemical [30] or neuroimaging [38] methods, which are not easily available in central european countries (in Poland and developing countries).

Multivariate analysis ensures more reliable conclusions concerning patient outcome and therefore, is often used in current studies. Most investigations concerning 30-day mortality predictors deferred consistent results. One group demonstrated that higher ESR, WBC count and hematocrit values were independent 30-day mortality rate predictors [27]. Another group demonstrated that the persistence of consciousness disturbances following 48 to 72 hours was the most important predictor and that a history of congestive heart failure lead towards a poor prognosis in fully conscious patients [13]. One study tried to determine prognostic factors during the first six hours following stroke in the carotid artery area and only noted the severity of the neurological deficit as an independent predictor of an increased mortality [8]. ECG and EEG abnormalities had been associated with an increased risk of early death in another study [14], while infarct size and limb paresis were predictive of a poor recovery. Two further studies confirmed the predictive role of atrial fibrillation [39, 43].

Other investigations have had different end-points yielding different predictive factors. One study analyzed a heterogeneous group of patients identifying increased age, hemorrhagic stroke, symptom resolution >72 hours and hyperglycemia, as predictors of mortality within three months following disease onset [44]. Another study established that an eight-day mortality depended only on the level of consciousness on admission, while death or dependence during the third month following stroke depended on the severity of the clinical deficit, a previous history of stroke and patient age [45]. Still another examined 300 non-comatose patients and accurately predicted death or disablement four months following stroke, using age and the neurological deficit within six hours after disease onset [46].

Due to the non-comparability of the strata of different populations, analyses results that use multiple regression models are difficult to duplicate [47]. Thus, we decided to investigate our own population.

Despite the inconsistencies mentioned above, we confirmed the crucial role of simple clinical and laboratory data which can be used in everyday situations.

CONCLUSIONS

Our study results, based on a well-defined, consecutive and relatively large group of patients with their first ischemic stroke, indicate that simple clinical data, such as a neurological deficit on admission or on the next day, decreased consciousness within 24 hours following stroke onset, or ECG evidence of dysrhythmia, are independent predictors of a higher 30-day mortality in stroke patients. These factors should help in considering patient management guidelines and plan future drug trials.

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